THE KIDNEY
IN HEALTH AND DISEASE

IN CONTRIBUTIONS BY EMINENT AUTHORITIES

EDITED BY

HILDING BERGLUND, M D

STOCKHOLM SWEDEN

FORMERLY CHIEF OF THE DEPARTMENT OF MEDICINE AT THE UNIVERSITY OF MINNESOTA MINNEAPOLIS MINN

and GRACE MEDES, PH D

RESEARCH BIOCHEMIST IN THE LANKENAU HOSPITAL RESEARCH INSTITUTE PHILADELPHIA PA

WITH THE COLLABORATION OF

G CARL HUBER, M D

PROFESSOR OF ANATOMY AND DIRECTOR OF ANATOMICAL LABORATORIES AND DEAN OF THE GRADUATE SCHOOL OF THE UNIVERSITY OF MICHIGAN ANN ARBOR MICH

WARFIELD T LONGCOPE, M D

PROFESSOR OF MEDICINE IN THE JOHNS HOPKINS UNIVERSITY BALTIMORE MD

ALFRED N RICHARDS, PH D, M D

PROFESSOR OF PHARMACOLOGY IN THE UNIVERSITY OF PENNSYLVANIA PHILADELPHIA PA

ILLUSTRATED WITH 163 ENGRAVINGS



LEA & FEBIGER

PHILADELPHIA

PRINTED IN U S A

PUBLISHERS' NOTE

This volume is the outgrowth of a symposium on the structure and function of the kidney in health and disease which took place in Minneapolis during the summer of 1930. The project was initiated by Dr Hilding Berglund then Professor of Medicine in the University of Minnesota and the social and financial responsibilities of the occasion were met by that institution. The programs were arranged and the speakers selected by Dr Berglund and the success of the undertaking was largely due to his energy.

The original plans included the publication of this material as soon as possible after the end of the symposium sessions and a large part of the work of assembling and editing it was done by Dr Berglund during the following year. To the great regret of all those concerned his return to Sweden prevented him from finishing this aspect of the work.

The Publishers became convinced that these contributions are sufficiently important to be preserved in permanent form that collectively they constitute a comprehensive and authoritative exposition of our present knowledge concerning a most important but still obscure field of medical science. For the purposes of the present volume the participants in the symposium have revised their contributions and amplified them to some extent to bring them up to date. Several contributions which were not included in the symposium have been added. The editorial work has been completed by Dr Medes with assistance from several of the contributors.

LIST OF CONTRIBUTORS.

M HERBERT BARKER M S M D
Associate in Medicine Northw [illegible]
of the Renal Clinic and R [illegible]
School Clinics Consultant [illegible]
Hines Hospital Chicago [illegible]
Hospital Chicago Ill

E T BELL, M D,
Professor of Pathology in the University of Minnesota Minneapolis Minn

HILDING BERGLUND M D
Stockholm Sweden

RAYMOND N BIETER, M D PH D
Associate Professor of Pharmacology in the University of Minnesota Minneapolis Minn

KENNETH D BLACKFAN M D
Professor of Pediatrics in the Harvard Medical School Boston Mass

JAMES BORDLEY III M D
Instructor in Medicine in the Johns Hopkins University Baltimore Md

GEORGE O BURR, PH D
Associate Professor of Plant Pathology in the University of Minnesota Minneapolis Minn

ALLAN M BUTLER M D
Instructor in the Department of Pediatrics of the Harvard Medical School Boston Mass

[illegible] f Minne[illegible] Mary s [illegible]

HAROLD S DIEHL M D M A
Director of the Department of Preventive Medicine and Public Health Director of the Students Health Service in the University of Minnesota Minneapolis Minn

JONAS S FRIEDENWALD A M M D,
Associate Professor of Ophthalmology in the Johns Hopkins University Baltimore Md

JAMES L GAMBLE M D
Professor of Pediatrics in the Harvard Medical School Boston Mass.

ALFRED GRUNBAUM CHEM D,
Conservator of the Laboratory for General Pathology in the University of Amsterdam Holland

ROGER ROBERT HANNON PH D M D
Associate in Medicine in the Rockefeller Institute Hospital New York City

A BAIRD HASTINGS, PH D,
Research Professor of Biochemistry, Lasker Foundation for Medical Research in the University of Chicago, Chicago, Ill

FRANK HINMAN, M D,
Clinical Professor of Neurology in the University of California, San Francisco Calif

G CARL HUBER, M D, Sc D,*
Professor of Anatomy and Director of Anatomical Laboratories and Dean of the Graduate School of the University of Michigan, Ann Arbor, Mich

C M JACKSON, M D, LL D,
Professor and Head of the Department of Anatomy in the University of Minnesota, Minneapolis, Minn

NORMAN M KEITH, M D,
Associate Professor of Medicine, Mayo Foundation, Rochester, Minn

LOUIS LEITER, M D, PH D,
Associate Professor in the Lasker Foundation for Medical Research and the Department of Medicine in the University of Chicago, Chicago, Ill

WARFIELD T LONGCOPE, M D,
Professor of Medicine in the Johns Hopkins University, Baltimore, Md

FRANCIS D W LUKENS, M D,
Jacques Loeb Fellow in Medicine in the Johns Hopkins University, Baltimore, Md

THOMAS BYRD MAGATH, M S, PH D, M D,
Consulting Physician in Clinical Pathology, Mayo Clinic, Associate Professor of Pathology, Mayo Foundation for Education and Research in the University of Minnesota, Minneapolis, Minn

E K MARSHALL, PH D, M D,
Professor of Physiology and Experimental Therapeutics, Johns Hopkins University, Baltimore, Md

CHAUNCEY A McKINLAY, M D,
Assistant Professor of Medicine in the University of Minnesota, Minneapolis Minn

GRACE MEDES, PH D,
Research Biochemist in the Lankenau Hospital Research Institute, Philadelphia

P BRANT REHBERG, PH D,
Ammanuensis at the Zoophysiological Laboratory in the University of Copenhagen, Denmark

HOBART A REIMANN, M D,
Associate Professor of Medicine in the University of Minnesota, Chief of Staff of the Medical Service in the University Hospital, Minneapolis, Minn

STANLEY P REIMANN, M D,
Director of the Lankenau Hospital Research Institute, Philadelphia,

*Deceased December 26 1934

A N RICHARDS Ph D, Sc D M D
Professor of Pharmacology in the University of Pennsylvania Philadelphia

LEONARD G ROWNTREE M D, Sc D
Director of the Philadelphia Institute for Medical Research

WALTER [illegible] SCRIVER M D C M F R C P (C)

HOMER W SMITH Sc D
Professor of Physiology in the University and Bellevue Hospital Medical College New York City

ISIDORE SNAPPER M D
Professor of Medicine and General Pathology in the University of Amsterdam Holland

H B VAN DYKE M D Ph D
Professor of Pharmacology in the Peiping Union Medical College Peiping China (formerly Professor of Pharmacology at the University of Chicago)

FRANZ VOLHARD M D
Professor and Director of the Medical Clinic of the University of Frankfurt Frankfurt on the Main Germany

HENRY P WAGENER, M D M S in Ophthalmology
Associate Professor of Ophthalmology in the Mayo Foundation of the University of Minnesota Minneapolis, Minn

WALTMAN WALTERS M D M Sc in Surgery
Surgeon in the Mayo Clinic Associate Professor of Surgery in the Graduate School of Medicine of the University of Minnesota Minneapolis Minn

MACNIDER WETHERBY M D
Instructor in Medicine in the University of Minnesota Minneapolis Minn

H L WHITE M D
Associate Professor of Physiology in the School of Medicine of the Washington University St Louis Mo

HAROLD N WRIGHT M S Ph D
Assistant Professor of Pharmacology in the University of Minnesota Minneapolis, Minn

CHAPTER IV

The Filtration Reabsorption Theory of Kidney Function and Its Use in the Clinic

By Paul Brandt Rehberg Ph D

CHAPTER V

The Excretion of the Non metabolized Sugars in the Dogfish, the Dog and Man

By Homer W Smith Sc D

CHAPTER VI

The Role of the Tubules in the Renal Excretion of Water

By H L White M D

CHAPTER VII

THE EFFECT OF THE SPLANCHNICS UPON GLOMERULAR BLOOD FLOW.
By RAYMOND N. BIETER, M.D., PH.D.

CHAPTER VIII

THE EFFECTS OF DIETARY DEFICIENCY ON RENAL GROWTH AND STRUCTURE
By C. M. JACKSON, M.D., LL.D.

CHAPTER IX

RENAL COUNTERBALANCE
By FRANK HINMAN, M.D.

PART II

CLINICAL ASPECTS OF RENAL FUNCTIONS

CHAPTER X

CERTAIN CHEMICAL ASPECTS OF RENAL FUNCTION
By JAMES L. GAMBLE, M.D.

CHAPTER XI

The Optimal Water Requirement in Renal Function

By James L Gamble M D

CHAPTER XII

The Non-excretory Functions of the Kidney

By Isadore Snapper, M D, and Alfred Greenbaum Chem D

CHAPTER XIII

The Phenolsulphonephthalein and Other Tests of Renal Function

By Leonard G Rowntree M D

CHAPTER XIV

The Blood Urea Clearance Test

By Roger R Hannon M D

CHAPTER XV

Studies in Rehberg's Creatinine Test for Glomerular Filtration

By Grace Medes, Ph D, and Hilding Berglund, M D
(In Partial Collaboration with E Blegen, M D)

CHAPTER XVI

RENAL INSUFFICIENCY
By FRANZ VOLHARD, M D

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION
By GEORGE O BURR PH D, and GRACE MEDES, PH D

PART III

BRIGHT'S DISEASE AND VARIOUS OTHER PATHOLOGIC RENAL CONDITIONS

CHAPTER XVIII

THE PATHOLOGY OF THE MAIN NEPHROPATHIES
By E T BELL, M D

CHAPTER XIX

CONGENITAL RENAL ANOMALIES
By STANLEY P REIMANN, M D

CONTENTS

CHAPTER XX

Infections of the Kidney

By Hobart A Reimann M D

CHAPTER XXI

Infection by Streptococci in Relation to Recovery and Progress in Nephritis

By Warfield L Longcope M D James Bordley III M D, and Francis D W Lukens M D

CHAPTER XXII

A Comparison of Blood-pressure in Men and Women A Statistical Study of 5540 Individuals

By Macnider Wetherby M D

CHAPTER XXIII

Elevated Blood pressure

By Franz Volhard M D

CHAPTER XXIV

BILATERAL NECROSIS OF THE RENAL CORTEX
By WALTER DE M. SCRIVER, M.D.

CHAPTER XXV

RENAL NEOPLASMS
By STANLEY P. REIMANN, M.D.

CHAPTER XXVI

KIDNEY TROUBLE IN ACUTE LUPUS ERYTHEMATOSUS
By ISIDORE SNAPPER, M.D.

PART IV

ALBUMINURIA AND EDEMA

CHAPTER XXVII

MINIMAL ALBUMINURIA AND TESTS FOR ALBUMIN IN THE URINE
By THOMAS B. MAGATH, PH.D., M.D.

CHAPTER XXVIII

ALBUMINURIA IN YOUNG MEN
By HAROLD S. DIEHL, M.D., and CHAUNCEY A. MCKINLAY, M.D.

CHAPTER XXIX

Orthostatic Proteinuria

By Grace Medes Ph D and Mary R Neemes, B S

CHAPTER XXX

Proteinuria and Plasma Proteins

By Hilding Berglund M D Walter de M Scriver M D and Grace Medes Ph D

CHAPTER XXXI

Bence-Jones Proteinuria

By Grace Medes Ph D with Partial Collaboration of Hilding Berglund M D and technical assistance of Mary R Neemes B S

CHAPTER XXXII

Salts and Edema

By A Baird Hastings Ph D

CHAPTER XXXIII

Edema in Dogs Following Sodium Bromide Administration

By A Baird Hastings Ph D and H B Van Dyke Ph D M D

CHAPTER XXXIV

RECENT DANISH WORK ON EDEMA
By PAUL BRANDT REHBERG PH D

CHAPTER XXXV

EXPERIMENTAL NEPHROTIC EDEMA
By LOUIS LEITER PH D M D

CHAPTER XXXVI

EXPERIMENTAL EDEMA THE EFFECT OF LOW PLASMA PROTEIN LEVEL UPON WATER BALANCE AS RELATED TO SPECIFIC IONS
By M HERBERT BARKER, M S M D

PART V

OCULAR CHANGES IN BRIGHT S DISEASE

CHAPTER XXXVII

RETINAL LESIONS IN NEPHRITIS AND HYPERTENSION
BY HENRY P WAGENER M D

CHAPTER XXXVIII

THE PATHOLOGY OF THE OCULAR CHANGES IN NEPHRITIS AND HYPERTENSION
By JONAS S FRIEDENWALD A M M D

PART VI.

CLINICAL ASPECTS OF BRIGHT'S DISEASE.

CHAPTER XXXIX

UREMIA

By FRANZ VOLHARD, M D

CHAPTER XL

TREATMENT OF ACUTE DIFFUSE GLOMERULONEPHRITIS

By FRANZ VOLHARD, M D

CHAPTER XLI

CEREBRAL SYMPTOMS IN ACUTE GLOMERULAR NEPHRITIS AND THEIR TREATMENT

By KENNETH D BLACKFAN, M D, and ALLAN M BUTLER, M D

CHAPTER XLII

FUNDAMENTAL STUDIES ON THE PHARMACOLOGY OF MERCURY DIURETICS
By RAYMOND N BIETER, M D, PH D, and HAROLD N WRIGHT M S, PH D

CHAPTER XLIII

THE CLINICAL USE OF DIURETICS
By NORMAN M KEITH M D

CHAPTER XLIV

NERVOUS RENAL CONTROL AND RENAL SYMPATHECTOMY
By LEONARD G ROWNTREE Sc D M D WALTMAN WALTERS Sc D, M D, and WINCHELL McK CRAIG M S F A C S

THE KIDNEY IN HEALTH AND DISEASE

PART I

ANATOMY AND PHYSIOLOGY

CHAPTER I

THE FORM AND STRUCTURE OF THE MAMMALIAN RENAL TUBULE

By G. CARL HUBER, M.D., Sc.D.

Introduction.—The relatively complex form and structure of the renal tubule of vertebrates has made of it, for over a century, the subject of repeated investigation. The difficulty of correlating structure and function has added to the interest of such studies and has called forth a long succession of physiological and pharmacological contributions of note. Repeatedly, both morphological and correlated functional studies appear to have led to definite conclusions only to find through further investigations that such conclusions were subject to revision. Interest is further added by the fact that both phylogenetically and ontogenetically considered the renal organs of vertebrates consist of three successive sets of excretory organs known as pronephros, mesonephros and metanephros; the pronephros functions in the lowest vertebrates and during larval stages of amphibia, the mesonephros in fishes and amphibia and the metanephros in reptiles, birds and mammals. The renal tubules of the phylogenetically serial excretory organs, while successively more complex, are fundamentally of very similar morphology and structure and appear in the main to function similarly, cognizance of which fact is taken in experimental work, in that it is possible to transfer deductions drawn from observations made on the simpler renal tubules of the amphibia to the more complex and less accessible renal tubules of mammalia. The similarity of form, structure and function of the renal tubules of the

pronephros and mesonephros to those of the metanephros necessitates a brief consideration of the former in anticipation of a further consideration of the renal tubules of the metanephros in its fullest development as in the mammal By means of the Born wax plate method of reconstruction it was possible to build up in wax at a magnification of 400 diameters the pronephric tubules of a larval

to mount in semipermanent form the renal tubules of birds and several mammals Thus *it is now possible to treat of the form* size and length of the vertebrate renal tubule in a much more satisfactory and comprehensive manner than was possible before such studies were undertaken The figures here given are based on actual preparations and are not to be regarded as diagrams or semidiagrammatic representations The measurements of length given are based on measurements made on models or on completely isolated and mounted renal tubules

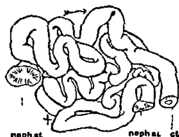


Fig 1 —Reconstruction of the pronephric tubules of a larva of Bufo having a total length of 10 mm *neph st* Nephrostomes *ct* common collecting tubule + region of the Y-shaped junction of the two tubules × 80 (Huber Cowdry's Special Cytology courtesy of Paul B Hoeber Inc

PRONEPHRIC TUBULES

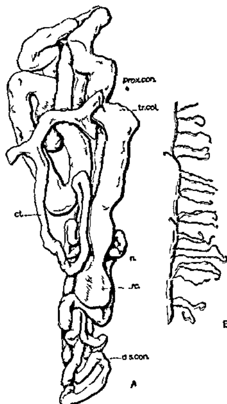
As a type of a functional pronephric tubule there is here depicted (Fig 1) a wax reconstruction of a pronephric tubule of a larval toad of 10 mm in length The tubule shown presents two nephrostomes opening into the celomic cavity and lined by cells with prominent cilia The tubules leading from the nephrostomes join in a Y shaped junction The tubule thus formed has a length of 2 5 mm and presents a series of loops which in the main extend in a craniocaudal direction The tubules reconstructed have their beginnings in nephrostomes and not in renal corpuscles with glomerular capillaries The *epithelium lining* the coiled portion of these tubules is of a low columnar type presenting a typical and prominent *brush border* while the protoplasm of the basal part of the cell

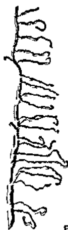
shows a vertical striation which appears to be due to the presence of coarse ectoreticular fibrils. Von Mollendorff[15] has shown, in experiments with vital staining with trypan blue, that the coloring matter found in the lumen of the tubules appears in globular form in the cells with brush border. The evidence presented seems to substantiate the contention that water and contained substances in solution are absorbed into the blood through the epithelial cells with brush borders lining the coiled portions of the tubules. This portion of the pronephric tubule may thus be homologized with the tubular segment known as the proximal convoluted tubule of higher forms.

THE MESONEPHRIC RENAL TUBULE

The mesonephric tubule has been known for many decades and was quite accurately described and figured by Nussbaum[16,17,18] based on observations made on teased preparations. The figures here given (Fig. 2) represent drawings of a model made by Born wax plate method and casts of the lumen of collecting tubules made after an especially devised celluloid-alkanin injection method. The main efferent duct of the frog's kidney, the ductus deferens, joins the kidney at its caudal end and, passing along its dorso-lateral border, reaches the cephalic end, where it becomes partly embedded in the kidney substance. At fairly regular intervals there empty into the ductus deferens at nearly right angles a series of transversely coursing collecting ducts embedded in the kidney substance near its dorsal surface. Into these nearly parallel transversely coursing collecting ducts there empty the mesonephric renal tubules in quite regular serial order. One such transverse collecting tubule with the terminal portion of a series of renal tubules is show[illegible] is seen in w[illegible] everal part[illegible] The tubule begins in a renal corpuscle and ends in a transverse collecting duct and has a total length of 7 mm. The renal tubules traverse the entire dorso-ventral thickness of the frog's kidney, the great majority of the renal corpuscles form an irregular layer situated near the ventral surface. Each renal tubule begins in a relatively large renal corpuscle of flattened oval form and averaging about 100μ in diameter, and consisting of a glomerular capillary complex and an invaginated glomerular capsule presenting a visceral and a parietal layer, the latter joining the renal tubule by means of a short neck. The visceral and parietal layers of the glomerular capsule are lined by a delicate layer of flattened pavement epithelium, while the neck is lined by relatively short non-pigmented cells supporting long cilia. The neck is followed by a tubular segment having relatively large diameter and extending toward the

dorsal surface of the kidney, there to form several bold loops which may extend to about the middle of the kidney substance This tubular segment constitutes the proximal convoluted portion and in the tubule shown in the figure presents an average diameter of 75 μ and a length of approximately 3 8 mm, and is lined by an epithelium of low columnar form with finely striated superficial brush border and relatively distinct basal striations apparently due to the presence of fine granules in the cytoreticulum The proximal convoluted portion is followed by a short and narrow segment (0 2 mm) comparable in position to the medullary loop of the mammalian renal tubule, and is lined by a low epithelium with delicate cilia The succeeding tubular segment which has been termed the distal convoluted portion, attains a length of approximately 2 5 mm and an average diameter of 30 μ and presents numerous coils and loops certain of which reach the ventral surface of the kidney and is lined by a low cuboidal epithelium presenting basal striations A short junctional tubule unites this distal convoluted segment with a transverse collecting tubule This junctional tubule is lined by a cuboidal epithelium similar to that lining the collecting ducts It is of interest to note that among teleosts are found forms whose kidneys possess very few or no glomeruli Such forms have been subjected to careful investigation both morphologically and func-





tionally relatively recently by Edwards,[4,5] Grafflin[7] and Marshall.[14] Edwards has shown that in an aglomerular kidney the mesonephric tubule is composed of three segments, the first of which is similar to the proximal convolution of the higher vertebrates, the second to the distal convolution and the third to a collecting duct.

THE METANEPHRIC TUBULE

A description of the metanephric renal tubule requires consideration of the renal tubules of reptiles, birds and mammal. The metanephric tubules of reptiles and birds will receive brief consideration before entering on a more detailed discussion of the mammalian renal tubule.

Reptilian Metanephric Tubules. The account of the morphology of the reptilian metanephric tubule is based on reconstruction and celluloid corrosion injections of the renal tubules and the duct system of a turtle, Alligator mississippiensis, garter snake and a lizard. The reconstructions made of the renal tubules of the several forms studied show such great similarity, except for unimportant differences in size and extent of looping, that a description of one of them obviates the necessity of describing the others. The account here presented is based on the metanephric tubule of a turtle, Chrysemys marginata, illustrated in A of Fig. 3. The renal tubules of Chrysemys marginata begin in relatively small renal corpuscles averaging approximately 50 μ in diameter, consisting of a relatively simple glomerulus enveloped by a glomerular capsule with visceral and parietal layer, the latter continuing as the neck, a short and narrow segment lined by an epithelium bearing long cilia. The renal corpuscles are centrally placed in pseudolobules of kidney substance. The neck is followed by the

lined by a ciliated epithelium which in position is the homologue of the medullary loop of the mammalian renal tubule. This segment is followed by the distal convoluted portion presenting a length of approximately 1 mm and an average diameter of 40 μ and lined by a low columnar epithelium with striated protoplasm. A short junctional segment unites the renal tubule to a primary collecting duct. The total length of the renal tubule figured in A of Fig. 3 is approximately 3.3 mm.

The Metanephric Tubule of Birds —In the study of the renal tubule of birds use was made of the kidneys of adult chicken Gallus domestica Use was made of especially devised methods of maceration and teasing The material was prepared for teasing by injecting the fresh kidney through the renal artery with a 75 per

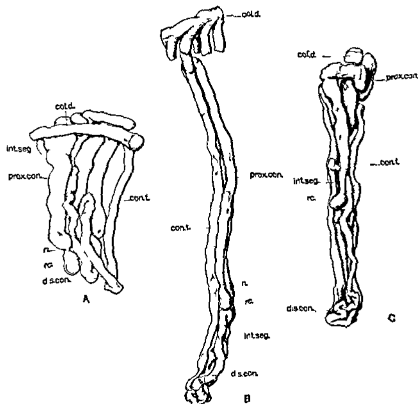


FIG 3 —Reptilian metanephric renal tubules A Reconstructed from the kidney

of Paul B Hoeber Inc)

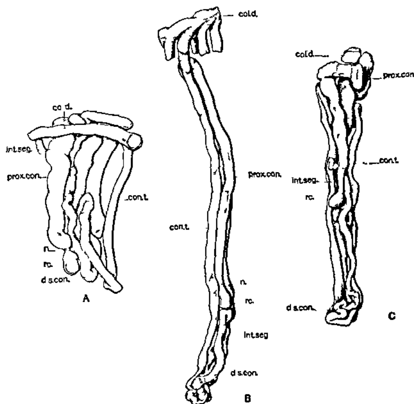
cent solution of hydrochloric acid at a pressure of about 20 pounds After the injection the tissue was placed in strong hydrochloric acid for several hours and then thoroughly washed in water stained in hematoxylin solution and prepared for teasing With adequate maceration it was found possible to isolate entire renal tubules attached to portions of the duct system and to mount such preparations in a semipermanent way ready for study under the micro-

scope The kidney of the bird is an elongated, distinctly lobulated organ, with the ureter passing on the ventral and meso-ventral side, prominent branches passing from the ureter to the several lobules The central portion of each lobule may be divided into a cortical and a medullary portion not unlike the mammalian kidney The cortex extends distinctly beyond limits of the central part of each lobule, this peripheral portion presenting an appearance not unlike that of the reptilian and especially that of the turtle kidney By use of the above-mentioned methods of maceration and teasing, it may be determined that the more peripherally placed tubules of a renal lobule present an appearance very much like that of the reptilian renal tubule, while those found in the core of the lobule resemble very closely the mammalian renal tubule, with transition forms as one passes from the periphery to the more central portion of the lobule This is evidenced in the several renal tubules shown in Fig 4 Tubule *A* of this figure presents a total length of approximately 6 5 mm It begins in a relatively small nearly spherical renal corpuscle The proximal convoluted portion of this tubule

mediate segment is followed by the distal convoluted portion, arranged in the form of a number of compactly placed small loops, from which extends a junctional segment leading to a primary collecting duct Tubule *A*, as shown in Fig 4 is mounted after

blance in form The tubule figured in *B* of Fig 3 presents a length of 13 mm of which approximately 7 5 mm fall to the prominent coil complex seen to the left of the figure and representing the proximal convoluted segment The beginning of a medullary loop is noticed as also a distinct distal convoluted portion In tubule *C* of Fig 4 is shown an avian renal tubule teased from the more central portion of a renal lobule and represents a very successful teasing and mounting of the more fully developed avian metanephric tubule The figure shows the form of this tubule so clearly that little discussion seems necessary The entire length is approximately 15 5 mm of which 8 5 mm fall to the proximal convoluted portion 3 8 mm to the medullary loop 2 2 mm to the distal convoluted segment and 1.2 mm to the junctional segment The tubule begins in a relatively large nearly spherical renal corpuscle

The Metanephric Tubule of Birds —In the study of the renal tubule of birds use was made of the kidneys of adult chicken Gallus domestica Use was made of especially devised methods of maceration and teasing The material was prepared for teasing by injecting the fresh kidney through the renal artery with a 75 per



of Paul B Hoeber Inc)

maceration it was found possible to isolate entire renal tubules attached to portions of the duct system and to mount such preparations in a semipermanent way ready for study under the micro-

scope The kidney of the bird is an elongated, distinctly lobulated organ with the ureter passing on the ventral and meso-ventral side prominent branches passing from the ureter to the several lobules The central portion of each lobule may be divided into a cortical and a medullary portion not unlike the mammalian kidney The cortex extends distinctly beyond limits of the central part of each lobule this peripheral portion presenting an appearance not unlike that of the reptilian and especially that of the turtle kidney By use of the above-mentioned methods of maceration and teasing, it may be determined that the more pheripherally placed tubules of a renal lobule present an appearance very much like that of the reptilian renal tubule while those found in the core of the lobule resemble very closely the mammalian renal tubule with transition forms as one passes from the periphery to the more central portion of the lobule This is evidenced in the several renal tubules shown in Fig 4 Tubule 1 of this figure presents a total length of approximately 6 5 mm It begins in a relatively small nearly spherical renal corpuscle The proximal convoluted portion of this tubule having a length of 3 8 mm is arranged in the form of a letter N each part of the N presenting numerous loops and coils The

mediate segment is followed by the distal convoluted portion arranged in the form of a number of compactly placed small loops from which extends a junctional segment leading to a primary collecting duct [illegible]

coil complex seen to the left of the figure and representing the proximal convoluted segment The beginning of a medullary loop is noticed as also a distinct distal convoluted portion In tubule *C* of Fig 4 is shown an avian renal tubule teased from the more central portion of a renal lobule and represents a very successful teasing and mounting of the more fully developed avian metanephric tubule The figure shows the form of this tubule so clearly that little discussion seems necessary The entire length is approximately 15 5 mm of which 8 5 mm fall to the proximal convoluted portion 3 8 mm to the medullary loop 2 2 mm to the distal convoluted segment and 1 2 mm to the junctional segment The tubule begins in a relatively large nearly spherical renal corpuscle

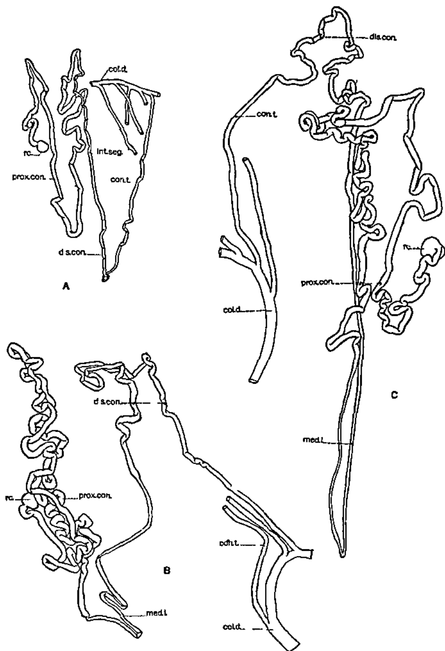


FIG 4 —*A* Metanephric renal tubule of bird Gallus domestica completely

The whole tubule in form sequence and relative position of parts resembles very closely a mammalian renal tubule

A discussion of the form and structure of the pronephric meso nephric and the simpler metanephric renal tubules has been introduced to show that while it must be recognized that one is dealing with a phylogenetically serially arranged excretory renal system which in ontogeny do not differentiate with successive stages of a single organ but with developmental and regressive stages in a series of organs each of which presents excretory tubules and a duct system there is nevertheless a very distinct resemblance both in the form and structure of the renal tubules of the different forms, especially as concerns the mesonephric and the simpler metanephric renal tubules In a typical renal tubule phylogenetically considered there are to be observed distinct regional cytological differentiations which may be serially enumerated as follows (*a*) The renal corpuscle consisting of an arterial capillary net the glomerulus enveloped by a double-walled glomerular capsule with visceral and parietal layer lined by delicate squamous epithelial cells and representing the invaginated end of the renal tubule (*b*) the proxi-

intermediate segment in the different forms varying greatly in relative length of small diameter and lined by low cuboidal or squamous cells which may or may not support cilia and in position comparable to the medullary loop of the more complex mammalian renal tubule (*d*) the distal convoluted segment of variable length and lined with low columnar epithelium with basal cytoreticular striations Exceptions to the above general statements are found in the nephrostome of the pronephric renal tubule which functionally appears to replace the renal corpuscle and the aglomerular renal tubules found in certain teleosts but even in such forms one may be able to determine with a variable degree of certainty the successive tubular segments with characteristic cytological differentiation as here enumerated

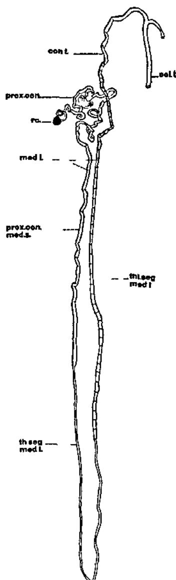
The consideration of pronephric mesonephric and the simpler metanephric tubules seemed also desirable by reason of the fact that a relatively large per cent of the more recent observations on renal secretion relate to the mesonephros of amphibia We may cite the outstanding work of Richards and his collaborators [20, 21] who have devised a technique for collecting glomerular urine from a single mesonephric glomerular capsule which has enabled them to compare glomerular urine with simultaneously collected bladder urine and the studies of Marshall and his collaborators[14] on the

functional activity of the aglomerular kidney of teleosts which while probably representing phylogenetically and ontogenetically degenerated renal tubules are nevertheless of fundamental importance The exposed ventral position of the renal corpuscles in the amphibian mesonephros admits of experimental work which it would be quite impossible to carry on even in the metanephric kidneys of reptiles and birds and aglomerular renal tubules are not found in forms having the metanephros

The Mammalian Metanephric Tubule —Our present-day conception of the form length and relative position of the several parts of the mammalian renal tubule is a composite of observations extending over many decades The personal names which in the older literature are found attached to different parts of the mammalian renal tubule may serve as an index of the steps through which our knowledge was acquired We read of the Malpighian corpuscle Bowman s cap
of Henle and the distal
Two methods have been
form of the mammalian renal tubule (*a*) The method of wax plate reconstruction especially effective in the study of the developmental and young stages of the renal tubule since in the models made it is possible to reproduce the several parts in their normal relations and (*b*) especially devised methods of maceration and teasing permitting isolation and mounting in a semipermanent way of completely teased renal tubules of the adult By such methods of teasing many tubules may be studied and the relations of their several parts determined even though the details of the topographical relations of the seve
may be destroyed as a result of
the type form and cytological s
tubule we shall base our description on a completely isolated and successfully mounted preparation of the renal tubule of an adult

proximal convoluted portion with the medullary segment the medullary loop the distal convoluted portion and the junctional tubule The mammalian renal corpuscle is of approximately spherical form and varies in diameter between about 100 μ to 200 μ its size being roughly correlated with the length of the respective renal tubule The glomerulus with its afferent and efferent arterial branch and the capillary net will receive discussion when the renal blood supply is considered The visceral layer of the glomerular capsule surrounds very closely the glomerulus and consists of a single layer of delicate squamous epithelial cells with slightly serrated borders At the vascular pole of the renal cor

puscle, visceral layer of the glomerular capsule becomes reflected into the parietal layer the epithelial cells of which are of flattened polygonal form and gradually become thicker as the urinary pole of the renal corpuscle is reached The squamous epithelium of the visceral and parietal layer of the glomerular capsule constitutes a distinctive variety of epithelium in the renal tubule It is to be postulated that the epithelium of the visceral layer over the glomerulus is deserving of especial consideration in a discussion of the function of the several epithelia of the renal tubule The renal tubule proper is attached to the renal corpuscle by means of a short neck an extension of the parietal layer of the glomerular capsule This continues as the proximal convoluted portion with medullary segment It forms that portion of the renal tubule presenting the greatest diameter 50 μ to 60 μ loops toward the periphery of the kidney cortex and ends in the peripheral zone of the medulla This tubule is lined throughout by an epithelium which presents specific cytological structure and is here designated renal epithelium Irrespective of the total length of the renal tubule which in the rabbit varies from about 20 mm to about 30 mm the length of the proximal convoluted portion is essentially the same in all renal tubules



approaching a length of 10 mm The cytological structure of the renal epithelium is not easily determined in that this epithelium quickly shows postmortem changes and appears to present different appearances *depending on the fixation and staining methods used*

The structural appearance also seems to vary dependent on the phases of physiological activity As seen in cross section the tubule of the proximal convoluted portion may present a relatively low epithelium with wide lumen or a high epithelium with relatively narrow lumen with transitional stages The cells possess relatively large nuclei of spheroidal shape In the supranuclear portion of the cytoplasm there is to be noted a delicate vertical striation designated as brush border characterizing renal epithelium The basal or hyponuclear portion of the cytoplasm presents a distinctly striated or rodded appearance thought to be due to the presence and the arrangement of granules in the cytoreticular threads Mitochondrial granules have been found distributed in the cytoplasm of the cells of the renal epithelium of the proximal convoluted portions of the renal tubule In the great majority of the mammalian renal tubules the medullary segment of the proximal convoluted portion extends for a short distance into the periphery of the medulla where the tubule becomes greatly reduced in diameter This *the thin segment of the medullary loop* presents a diameter which varies from 20 μ to 25 μ and is of very variable length It is lined by squamous epithelium the cells having polyg onal form and relatively large nuclei and appearing thicker at their center than at their

loop varies greatly

with the relative p

the kidney In renal tubules having renal corpuscles situated near the periphery of the cortex the thin segment of the medullary loop is relatively short while in renal tubules having renal cor puscles situated in the depth of the cortex near the boundary of the medulla the thin arm of the medullary loop is relatively long with intermediate stages In the kidney of the adult rabbit the variation of the length of the thin segment of the medullary loop falls between about 1 and 15 mm In the renal tubule of the rabbit s kidney the thin segment of the medullary loop may be *found entirely on the proximal side of the loop may extend into the* loop or it may embrace the loop forming a portion of both the proximal and distal arms This thin arm of the medullary loop is followed by a segment which includes the greater portion of the distal limb of the medullary loop and the distal convoluted portion

either in the proximal

f or in the distal limb

varies between 30 μ

and 40 μ and is lined by a low columnar or cuboidal epithelium

presenting a clear supranuclear zone of cytoplasm devoid of brush border but with basal striation due to the presence of granules in the cytoreticulum though these are not quite so distinct as those found in the renal epithelium Mitochondrial granules have been found in the cytoplasm of the cells of the distal convoluted portion The distal convoluted portion joins the primary collecting duct through a junctional tubule with epithelium like that of the collecting ducts It is evident from this discussion that there are to be found four distinctive epithelial types in a mammalian renal tubule these are (*a*) The squamous epithelium of the glomerular capsules (*b*) the renal epithelium of the proximal convoluted portion with the medullary segment with brush border and basal striation (*c*) the squamous epithelium of the thin segment of the medullary loop and (*d*) the short columnar or cuboidal cells of the thick segment of the medullary loop and the distal convoluted portion with basal striation but devoid of the brush border

The primary collecting ducts of the cortex of the kidney either unite in the periphery of the cortex to form collecting tubes which pass through the cortex without receiving further branches or a limited number of primary collecting tubes join in the periphery

dichotomously in two successive divisions so that each forms four collecting ducts of the tenth order each of which passes into the cortex without further division there to branch further and to

Throughout the duct system cells with clear protoplasm ions and with relatively large nuclei of spherical or ovoid form The mammalian kidney substance after requisite maceration can be separated into slender pyramidal masses involving both cortex and medulla to which the term pseudolobuli has been given The apex of such a pseudolobule is formed by a collecting duct of the eighth order The four unbranching collecting ducts of the tenth order pass through the medullary portion of the pseudolobule and around them and between them are found the medullary loops of the renal tubules *collectively constituting a renal pseudolobule* *The cortical portion* of a pseudolobule continuous with that of the medulla has the form of a truncated pyramid in which the collecting ducts and the straight portions of the renal tubules occupy an axial position surrounded by the convoluted portions of the renal tubules The renal corpuscles are thus found at the periphery of the cortical

portion of a renal pseudolobule By reason of the fact that a mammalian renal tubule corresponds to a type form composed of serially arranged tubular segments each having a specific epithelial lining and consequent differences of diameter and transparency, the kidney substance composed of such renal tubules and especially is this true of the medulla, becomes divisible into zones which have been especially designated by Peter According to this observer, the medulla is divisible into an outer and inner zone the outer zone being further divisible into an outer and inner stripe The boundaries of these zones and stripes are dependent on structural changes occurring in the epithelium lining the renal tubules at respective levels The boundary between the outer and inner stripe of the outer zone lies in the region of change from the thick tubule of the medullary segment of the proximal convoluted portion to the thin segment of the medullary loop and the boundary line between the outer and inner zone falls to the region of the change from the thin segment of the medullary loop to the thicker segment of the thicker distal ascending portion of the medullary loop The general arrangement of the parts of the renal tubules and ducts of a pseudolobule and the relations of the several parts of the renal tubule to the zones and stripes of the medulla are portrayed in Fig 6 In renal tubules from the kidneys of an adult rabbit completely teased and mounted with renal corpuscles relatively placed as in the three renal tubules shown in Fig 6 namely, periph

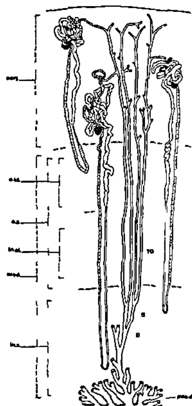


FIG 6 —Diagram of mammalian renal tubules with collecting duct system indicating topographic relations of the different tubular segments and their relations to the medullary zones as given by Peter Diagram based on reconstructions and teased preparations and refers in the main to human renal tubules *cort* Cortex *in st* inner stripe *in z* inner zone *med* medulla *o st* outer stripe *o z* outer zone *pap d* papillary ducts terminating in renal calyx *8 9* and *10* refer to the respective successive divisions of the collecting tubule including such divisions as are absorbed into the developing renal pelvis Collecting ducts of the eighth generation form the apices of renal pseudo lobules (Huber Cowdry s Special Cytology courtesy of Paul B Hoeber Inc)

to the long tubule with the renal corpuscle placed deep in the cortex

TABLE 1

	A mm	B mm	C mm
Proximal convoluted portion with medullary segment	11 3	9 4	10
[illegible]	1 4	6 7	15 0
convoluted portion (Cubic or short columnar epithelium	7 8	6 9	3 6
Total length of tubules exclusive of collecting duct	20 5	23 0	28 8

The ultimate distribution of the bloodvessels within the kidney and the relations of the terminal capillaries to the renal tubule deserve special consideration since the opinions maintained relative to these conceptions cannot help but influence very materially the views taken with reference to the functional activity of the different parts of the mammalian renal tubule In the mammalian kidney the renal artery as it enters the renal sinus divides into anterior and posterior branches which on further division enter the renal lobes coursing beneath the cortex in the form of branches designated arcuate arterial branches From the convex side of these arcuate arteries and at relatively close intervals are given off moderately branching terminal arteries which pass into the cortex as radiate arteries and in course give origin to afferent glomerular branches collectively furnishing a very rich blood

to the renal corpuscles to form glomerular capillary nets It is a [illegible]

the vas afferens breaks up into a capillary network as clearly shown in the reconstructions figured by Johnston and distinctly evident in well injected celluloid corrosion preparations The capillaries of a glomerulus collect to form an arterial efferent glo [illegible]

ing the rate of the blood flow through the glomeruli The efferent glomerular arteries of the several lower tiers of renal corpuscles divide into long slender arterioles and capillaries which pass into the medulla surrounding the medullary loops of the renal tubules and the collecting ducts and known as *arteriolæ rectæ* The efferent glomerular branches issuing from the remaining renal corpuscles redivide to form close meshed capillary nets which surround the convoluted portions of the renal tubules and the tubules of the cortical medullary rays The arteriolæ rectæ and the cortical capillaries pass into tributary veins Therefore essentially all of the blood which in capillary nets surrounds the different parts of the renal tubules is blood which has first passed through the renal corpuscles and during passage has given off water mineral salts and organic constituents to form glomerular urine

Extensive use has been made of the so-called vital stains in attempting to analyze and determine the process of renal tubule secretion The fact that the renal epithelium of the proximal convoluted tubule with medullary segment can be stained by use of certain vital stains has been interpreted as indicative of an excretory function of this epithelium Through methods devised by Richards and his collaborators [20, 21, 23] and used in obtaining glomerular urine it was found possible to introduce vital stains into the intracapsular space of a renal corpuscle without injuring the glomerulus and later by histological methods determine the presence of the stain in the protoplasm of the cells of the renal epithelium lining the proximal convoluted tubular segment Accumulating evidence permits the interpretation that the presence of stain in the renal epithelium is not proof of the secretion of said stain through the epithelium since stain introduced into the renal

dilution through the renal corpuscle Von Mollendorff [5] has given a comprehensive review of the numerous contributions dealing with the excretion of stains

and metanephric renal

subject Evidence is ε

a resorption of substances which through selective transudation pass through the visceral layer of the glomerular capsule in very great dilution The substances to be transudated into the renal capsule are thought to preexist in the blood plasma within the glomerular capillaries and it is postulated that they are not transformed in passage through the endothelium and through the epithelial layer of the visceral lamina of the glomerular capsule The proximal convoluted segment in pronephric mesonephric and metanephric renal tubules forms a conspicuous tubular segment present

ing great similarity in relative length and in epithelial lining, which epithelial lining is constituted by the renal epithelium with brush border and basal striations, and experimental evidence warrants the conclusions that in renal tubules with renal corpuscles and glomeruli water, inorganic salts and organic compounds are reabsorbed to a large extent in this tubular segment and that in this way glomerular urine begins to assume the form of bladder urine. A discordant note seems to be introduced by observers who have studied the structure and function of the renal tubules in aglomerular kidneys. Obviously in the renal tubules of such kidneys there cannot be formed glomerular urine, and the evidence seems fully to warrant the conclusion that in aglomerular renal tubules the epithelium of the proximal convoluted segment acts as a secretory epithelium. Observations on the functional activity of renal tubules of aglomerular kidneys are of interest and are important, but there does not appear evidence that warrants the deduction that renal tubules with renal corpuscles and functional glomeruli function in the same way as do aglomerular renal tubules.

There is at hand indirect evidence that fluid and salts are resorbed during the passage of the urine through the lumen of the thin segment of the medullary loop. As has been noted above, the length of this segment varies within wide limits as measured on completely teased renal tubules from the kidney of a rabbit, namely, from less than 1 to 15 mm. This wide range in the variation of th[illegible] p would in itself [illegible]ctional activity [illegible] segment of the [illegible] pre[illegible]ents struc-tural characteristics suggestive of an absorbtive function, perhaps active in the absorption of threshold substances.

Within the past decade a number of experimental workers have become enticed by the evidence in favor of the filtration and reabsorption theory as giving the most satisfactory explanation of the excretory mechanism of the renal tubule, and confirmatory experimental evidence appears to be accumulating, although it must be recognized that there is by no means unanimity in this interpretation of the mechanism of renal secretion. Recent observations of Bensley and Steen[2] in which experimental work of Nussbaum[16, 17, 18] and others on renal secretion after ligation of the renal artery in the frog, producing a glomerular inactivity, gave evidence which warranted ascribing specific secretory activity to the proximal convoluted tubule of the frog. They recognize the formation of

Thus there is still opportunity for further experimental morphological and experimental observations

References

1 Bensley R R 1929 The efferent vessels of the renal glomeruli of mammals as a mechanism for the control of glomerular activity and pressure Am J Anat 44 141 169
2 Bensley R R, and Steen W B 1928 The function of the differentiated segments of the uriniferous tubule Am J Anat 41 75–96
3 Cushny A R 1925 The Secretion of Urine London Longmans Green & Co
4 Edwards J G 1928 Studies on aglomerular and glomerular kidneys I Anatomical Am J Anat 42 75–107
5 ——— 1929 Studies on aglomerular and glomerular kidneys III [illegible]

piscatorius Am J Anat 44 441–4 [illegible]
8 Huber, G C 1905 On the development and shape of uriniferous tubules of certain of the higher mammals Am J Anat 4 (Suppl), 1 98
9 ——— 1907 The arteriolæ rectæ of the mammalian kidney Am J Anat 6 391–406
10 ——— 1910 The morphology and structure of the mammalian renal tubule *Harvey Lecture Philadelphia* J B Lippincott Company
11 ——— 1911 A method for isolating the renal tubules of mammalia Anat Rec 5 187 194
12 ——— 1917 On the morphology of the renal tubule of vertebrates Anat Rec 13 305–339
13 ——— 1928 Renal tubules Special Cytology edited by E V Cowdry New York Paul B Hoeber
14 Marshall, Jr E K 1929 The aglomerular kidney of the toadfish [illegible]

tat der Farbstoffe ihre Niere Anat Hefte 53

51–5[illegible]
16 Nussbaum M 1878 Ueber die Secretion der Niere Pfluger s Arch f d ges Phys 16 139–143
17 ——— 1878 Fortgesetzte Untersuchungen uber die Secretion der [illegible] 17 580–594

u und die Thatigkeit der Drusen f mikr Anat 27 442–480
uber Bau und Entwickelung der

nd results of direct invest gation of the tures Baltimore Williams & Wilkins

Company pp 63
21 Richards A N and Schmidt C F 1922 The glomerular circulation [illegible] 59 489–490

CHAPTER II

URINE FORMATION IN THE AMPHIBIAN KIDNEY

BY A N RICHARDS PH D SC D M D

THE NATURE OF GLOMERULAR FUNCTION

In order to prove that filtration is the sole process responsible for the separation of fluid from the blood in the glomerular capillaries it is necessary to show (1) That the head of blood pressure

If any authentic exceptions to these requirements are encountered we must conclude that another process or processes (secretion) must be concerned in the formation of glomerular urine Evidence on these three points is presented in order

1 **Glomerular Capillary Pressure** —The first effort to measure glomerular capillary pressure directly of which the author is aware was made by Hill[8] in 1921 He prepared the frog s kidney for direct microscopic observation squeezed a portion of it between

measurement represented the height of the capillary blood pressure and having found it to be somewhat lower than the osmotic pressure of plasma proteins he concluded that the glomerular process is not one of filtration

The second attack on this problem was made by Hayman[6] Two observations on the frog s kidney had previously been made which led to the method of direct measurement which he adopted (1) When a solution of a dye is injected into the intracapsular space the tubule originating from it can be accurately identified in the mass of tissue under observation as the colored solution flows

injecting pipette to measure the pressure just sufficient to arrest

blood flow through a fraction of the glomerular capillaries This pressure was taken to be equal to the mean pressure within the glomerular capillaries

The results of more than 150 measurements showed that the average glomerular capillary pressure (20 cm H_2O) was about 54 per cent of the average systolic aortic pressure (37 cm H_2O) Since the average value of the osmotic pressure of frog s plasma proteins was found by White to be 10 cm H_2O, it is obvious that Hayman s results pointed to an excess of capillary blood-pressure amply sufficient to permit the filtration of a protein-free fluid through the capillary walls

A third series of measurements of glomerular capillary pressure was made by White[37] He studied *Necturus maculosus*, adopting the method used by Hayman From the 22 experiments included in his first group 13 can be selected in which the glomerular circulation is reported as fair good or excellent Glomerular capillary pressures in these ranged from 10 1 to 26 5 cm H_2O, average, 16 15 In addition White measured the colloid osmotic pressure of the plasma from each of his animals and found that it varied from

Hayman
Hill The

question
l pressure

caused retardation of the movements of corpuscles through the glomerular capillaries and implies that the normal capillary pressure must, therefore be equal to or less than this He applied the

vessels of the glomerulus were tributary Surely the least degree of pressure applied to such a surface which was sufficient to increase *resistance* to flow in these veins and capillaries must have retarded flow through the glomerular vessels proximal to these, because of the relatively vast extent and distensibility of the rest of the frog's vascular system

In a paper published seven years later, Hill[9] states that the external pressure was applied quickly and that the criterion was momentary checking of glomerular blood flow, that the average of a "very large number of observations was 8 mm Hg The purpose of the suddenness of the application was to avoid what he

calls the "banking up" of pressure from the arterial side If the exact pressure required to collapse the glomerular capillaries could

measured Hill has given no adequate information on these points.

Another reason for distrust of Hill s results and confidence in those of Hayman and White can be found in a comparison of his estimations of mesenteric capillary pressures in the frog with those of Landis [11] The method which Landis used is exquisitely simple and direct It consists in the introduction of the tip of a micropipette directly into the lumen of the capillary studied or into one of its collaterals together with measurement of the pressure at which equilibrium exists between the fluid in the pipette system and the blood in the capillary The most frequent figure which Landis obtained for capillary pressure in the frog s mesentery was 13 cm H_2O Hill's figure was 8 mm Hg—exactly the same as for the glomerular capillaries The difference between Landis' figure for mesenteric capillaries 13 cm , and Hayman s figure for glomerular capillaries, 20 cm , is of the order which might be expected by reason of the interposition of the narrow efferent vessel between the glomerular capillary tuft and the intertubular capillaries

The adequacy of glomerular capillary pressure to permit the filtration of protein-free fluid against the opposing influences of intracapsular pressure and osmotic pressure of plasma proteins seems to me to have been convincingly proved by the work of Hayman and of White

2 Does separation of fluid from blood in the glomerulus cease when the glomerular capillary pressure sinks below the sum of intracapsular pressure plus osmotic pressure of plasma proteins?

The claim has been made by White[37] that the answer to this question is negative and he has drawn the conclusion that both secretion and filtration are operative in the glomerulus His experiments are the only ones of which the author is aware in which this question has been directly studied

He studied the kidney of Necturus In this animal each renal tubule is connected with a nephrostome which opens into the body cavity After having identified by the dye injection method a glomerulus and tubule appropriate for study, he closed the mouth of the nephrostome by cauterizing it, blocked the proximal tubule at a point distal to its juncture with the nephrostome and then inserted a micropipette into the intracapsular space Connected with the pipette was an adjustable reservoir of water, and this was raised to such a height that the sum of the intracapsular pressure plus the colloid osmotic pressure of the blood was greater than the

glomerular capillary pressure which had previously been measured Thus he reduced the effective filtration pressure in the glomerulus to less than zero He then observed in each of 7 experiments that a small bubble of air introduced as a pressure indicator into a horizontal tube connecting the pipette with the pressure reservoir moved slowly away from the tip of the pipette indicating that fluid was entering the pipette system from the glomerulus

If this result could be accepted at its face value it would be conclusive proof of the glomerular separation of fluid from the blood as the result of some process which is not filtration The author has not seen nor has he yet attempted to repeat White s experiments The number of variables however in this experiment which must be known and controlled seems to him to be greater than White has considered Before his conclusion is accepted assurance is desirable on such questions as these

(*a*) Is it not possible that the permeability of the glomerular membrane is altered at the beginning of the experiment by the interruption of blood flow necessary for determining glomerular capillary pressure and also during the course of the experiment by the retardation of blood flow consequent upon maintained increase in intracapsular pressure?

(*b*) Is it certain that the tonicity of the salt solution with which the pipette was filled was the same as that of the blood plasma? If it were higher diffusion from blood to capsular contents would give the result which White found

(*c*) Is there an hysteresis of the capsule of Bowman and of the other structures which constitute the walls of the closed system with which the pipette is connected which might result in a lag in return to their original tension following the excessive pressures to which they were subjected in the initial steps of the experiment?

(*d*) Can specific assurance be given on such obvious details as uniformity of caliber of the index tube its precisely horizontal position and absence of temperature inequalities in the system?

The author raises these question not he thinks because of

to 0 09 c mm per three
to five-minute inte *in one*
of his experiments pressed
by a trivial increase in intracapsular pressure (1 mm Hg)

From these considerations the author believes that a sound conviction of the existence of processes of glomerular secretion cannot at present be based upon White s experiments *

* The results of experiments made by Dr Whi e subsequently have led h m to a conclusion s m lar to th s (Am J Phys ol 102 2?2 1932)

3 Comparisons of the composition of blood plasma and glomerular urine

The first direct information was obtained by Wearn and the author in experiments with frogs[11]. It was qualitative rather than quantitative and so far as it went agreed with the filtration conception. Fluid collected from a renal corpuscle was free from protein; its reaction was on the alkaline side of neutrality; and it contained urea, sugar, chloride and also the dyes indigo-carmine and phenol red if these were injected into the circulation during the experiment.

Particularly impressive were the findings of sugar and chloride in glomerular fluid for the reason that neither was contained in measurable amounts in the urine which issued from the ureter. The observation provided the strongest evidence in support of reabsorption from the tubule and—more important for our immediate concern—showed that the glomerular process, whatever its nature, is not one which takes heed of the physiological necessities of the body for retaining sugar and chloride. Later White and Schmitt[33] obtained similar results in a study of the composition of glomerular fluid from Necturus.

They then ventured to attempt quantitative study of the composition of the glomerular fluid. The project which seemed hopelessly difficult at first has now been carried to a point where some satisfaction is to be derived from the results.

The first study was directed at the chloride content of glomerular fluid[33]. After a long discipline in the rigorous requirements of T. W. Richards' nephelometric method for estimating Cl they believed themselves capable of consistently estimating Cl in amounts of known solutions approximately as minute as the amounts of glomerular fluid with which they were obliged to deal. Seven out of 10 comparisons of frogs' glomerular fluid and plasma indicated that the Cl content of glomerular fluid was significantly higher than that of plasma. This unexpected result was published with no thought that it constituted a final answer to the question but as representing an initial attempt at a difficult problem which they hoped to attack again. Two years later Freeman, Livingston and the author renewed the study[8]. Estimations of Cl were made on glomerular fluids collected from 19 frogs perfused with Ringer's solution and from 20 living frogs. The outcome of the perfusion experiments was not ambiguous; no evidence was obtained of glomerular secretion of chlorides. The group of 20 living frog experiments contained 8 in which the Cl content of glomerular fluid appeared to be significantly higher than that of the plasma.

The net result of this second series was indecisive. We were quite uncertain which results represented the truth—the relatively few which might be interpreted as evidence of secretion of chloride

or the majority which pointed to identity of chloride content of the glomerular fluid and plasma For this reason, and for the reason that they intended a second repetition of the work, these results were not then published

The second paper which was published on the quantitative aspects of glomerular fluid was by White[36] He possessed the combination of information and insight which led him to believe that Barger's micromethod for estimation of molecular weights could be successfully applied to the present problem The method depends upon the fact that when minute droplets of different solutions of the same substance are placed in juxtaposition in a capillary tube, solvent will pass from the less to the more concentrated droplet White collected blood plasma and glomerular fluid from Necturus and introduced droplets of each into capillary tubes, according to the Barger method, measuring the length of the droplets immediately after the preparation of the tubes and again after the lapse of from eighteen to forty hours In each of 12 experiments he found that the droplet of glomerular fluid increased in length at the expense of the droplet of plasma thus indicating that glomerular fluid is more concentrated than plasma

At the same time that White's work was in process, Dr A M Walker and the author were engaged in attempts to estimate quantitatively the elimination of certain dyes in the glomerular fluid[8] The author had previously learned that satisfactorily accurate estimations of the concentration of phenol red in dilute solutions could be accomplished with exceedingly minute volumes of fluid provided the color comparisons with known standard solutions were carried out in capillary tubes of the same caliber Applying this method to glomerular urine collected from frogs' kidneys subjected to aortic perfusion with diluted horse serum to which phenol red had been added, it was found in preliminary experiments that glomerular concentration of the dye was as high as or higher than that in the perfusion fluid whereas when the same serum was filtered through collodion the concentration of phenol red in the filtrate was only 40 per cent of that in the serum, 60 per

the tubules Experiments designed to test this possibility showed that it was real, hence the procedure was modified to include obstruction of the renal tubules close to the glomerulus before beginning collection of the glomerular urine When the perfusion experiments with dilute horse serum were repeated with this modification, the concentration of dye in the glomerular fluid was precisely the same as that in an ultrafiltrate from the perfusion fluid

Turning then to living frogs which at the beginning of the experiment had been injected with small doses of phenol red it was found in a series of 14 experiments that glomerular concentration of this dye is the same as that of an ultrafiltrate from the frog s plasma

A few *similar experiments in which indigo-carmine was used* yielded a similar result

So it is apparent that at a time when White s confidence in the author s chloride results was being strengthened against his expectation by his own work on total molecular concentration the author s confidence in the same results was being shaken by the outcome of his dye experiments

This led to a decision by Walker to study the Barger method as described by White and to apply it to material collected from the frog [3] Thirty-one collections of glomerular urine were made and compared with plasma in Barger tubes Subtracting those in which known technical faults had been identified the results were consistent in showing essential identity in concentration of the two fluids The contradiction between these results on frogs and those of White on Necturus seemed to demand that Walker devote himself to the study of glomerular fluid obtained from Necturus This he did in 12 experiments with results which consistently confirmed those which he had obtained in frogs

Toward the close of this study by Walker beginnings of another sort were made as a result of the belief by Dr L E Bayliss that he could construct a conductivity cell suited to the measurement of electrical conductivity in very minute volumes of fluid This was accomplished and with Walker s aid in collecting the glomerular urine and plasma two series of experiments were completed by Bayliss one on frogs and one on Necturus [4] The outcome of these agreed with the outcome of the molecular concentration experiments by Walker Twenty six experiments were made on frogs 13 of these were regarded as technically perfect In these the difference in electrical conductivity between glomerular fluid and plasma was found to be of the same order as that encountered between plasma and ultrafiltrates from it Thirteen other experiments in which one or another minor defect was identified did not alter the conclusion drawn from the first group

Glomerular fluid from Necturus was studied in 15 experiments 10 of these were regarded as perfect and in these the total electrolyte concentration of the glomerular urine was indistinguishable from that of an ultrafiltrate from plasma

In recent months Dr Walker has been occupied with a project which the author has long hoped would be accomplished and in which a beginning was made by Wearn and the author ten years ago namely *the quantitative estimation of urea in glomerular*

fluid[33] An adaptation of the methods of Benedict and of Folin for urea estimation was made which was found to be reasonably accurate for amounts of urea nitrogen of the order of 0 0005 mg In a few experiments this method was applied to glomerular fluid from frogs Walker s plans took a different direction He conceived that it migh
urea
it
tube
bubl
glomerular fluid or urea solution in the capillary tube and of the increase in length of the bubble of air resulting from the nitrogen set free by the hypobromite were the only measurements required

In order to test the method 177 estimations were made on known urea solutions of various concentrations In 90 of these the results were within 10 per cent of being correct in 129 they were within 15 per cent and in only 9 did the values found differ from the true values by more than 25 per cent When a curve of averages was made from the entire series it was found to coincide exactly with the curve of known concentrations of the solutions taken

Forty four experiments on living frogs were made in which the urea concentration of glomerular urine was compared with that of plasma In 22 of these the former value was higher in 22 it was lower The average of all the glomerular urine values was 1 3 per cent higher than the average of the plasma values and when the curve of all the plasma urea values is made the dispersion of the glomerular urine urea values from this is such as to indicate identity of urea content of the two fluids

If a summary be made of the quantitative comparisons which have been described it will be seen that the great majority of the data point to identity of composition of glomerular urine and pro tein free plasma both in frogs and Necturi The comparisons include total molecular concentration total electrolyte concentra tion chloride urea and injected dyes

Before deciding that we are justified in adopting even tentatively the conclusion based on the majority of results we must decide whether good reasons exist which justify the setting aside of the divergent minority

The two divergencies which concern us are to be found among the estimations of total molecular concentration and of Cl In every one of White s 12 experiments the glomerular fluid appeared [illegible] than the plasma the outcome of Walker s [illegible] of the [illegible] author to suspect that he may have underestimated the opportunities for

evaporation of his samples during the manipulations incident to the measurements and special experiments by Walker on this point show that it is extremely important For this reason the author feels that Walker s results are the more credible

Of the ~ show higher Cl of this discrepan itative methods yet applied in these experiments that for Cl is most difficult and most beset with opportunity for error It is to be observed too that divergent Cl results are inconsistent not only with an equal number of other Cl estimations but also with the outcome of Bayliss series of total electrolyte studies and Walker s studies of total molecular concentration If chloride were actually as highly concentrated in glomerular fluid as it seemed to be in one-half of the experiments it is incredible that striking differences in total concentration should not have been more frequently encountered Finally it should be remembered that the frog s kidney possesses extraordinary power of preventing excretory loss of Cl from the body and that this power resides in the capacity of the tubule to restore to the blood Cl which has been eliminated in the glomerulus It is difficult to believe in the absence of unequivocal

the belief that in frogs and Necturi the composition of glomerular urine is indistinguishable from that of a protein free filtrate from plasma *

The question may properly be raised whether conclusions derived from the study of glomerular functions in the frog s kidney or in

study can determine

The purpose which the experimentation described in the foregoing pages was designed to serve was the acquisition of data which are capable of only one interpretation It is disappointing to find

101 193 3 39 255 1933)

that the verdict is not unanimous On the whole however, in view of the great technical difficulties it may be regarded as satisfactorily so as could have been expected It coincides with the verdict which has emerged from a great volume of experimental evidence obtained by different methods on different animals—evidence drawn from considerations of the anatomy of the glomerulus, from relations between renal blood pressure and volume of urine formation from the relation between osmotic pressure of blood-plasma and urine formation and from the study of the metabolism of the kidney under differing conditions of urine formation

THE REGULATION OF GLOMERULAR FUNCTION

Proceeding from the belief that the facts at present available

factors as most important

1 Glomerular blood-pressure considered in relation to the colloid osmotic pressure of blood plasma and intracapsular pressure, *i e* effective filtration pressure (White)

2 Rate of blood flow through the kidney *i e* rate of renewal of blood in contact with the glomerular endothelium

3 Permeability of the glomerular membranes

4 Extent of filtration surface

A satisfactory account of this subject would include not only an identification of the influences which are capable of affecting each of these factors but an evaluation of the extent to which each may be effective and an exposition of the interrelationships among them It need scarcely be said that the author can give no such exposition as this Our knowledge is as yet too fragmentary to justify the attempt The best we can do is to exhibit evidence which has enabled us to identify the separate operation of these factors and to strive for means of discovering how they may be studied more fruitfully in the future

1 **Glomerular Blood pressure** Early in the history of experimental study of renal function the gross relationships between *Ludwig*
Claude
gave a
untered

to the rule that urine formation varies directly with arterial blood pressure Anyone who has had experience in the study of vascular changes in various organs by means of the oncometer will agree *that the kidney ranks high in its capacity to undergo vasoconstriction*

in response to chemical or reflex stimulation of the vasoconstrictor

It was less easy to demonstrate the existence of a vasodilator nerve supply to the kidney But Bradford showed in 1899 that when the eleventh to the thirteenth dorsal fibers were stimulated by slowly repeated shocks renal vasodilatation occurred Dilatation of the renal bloodvessels in respon e to chemical agencies is however very easy to demonstrate *e g* urea glucose NaCl $NaHCO_3$ Na_2SO_4 $NaNO_3$ etc All of the substances which we class as diuretics dilate the vessels of the kidney

The statements above provide the basis for what may be called gross explanations of changes in urine elimination secondary to

example as are associated irritation severe muscular It has become possible

however to enlarge our conceptions of alterations of renal blood

showed that a minute change in the CO_2 content of alveolar air caused a relatively tremen lous increase in the volume of respiration similarly slight changes in the composition of the blood almost too small to be recognized by analytical methods are followed by seemingly disproportionate alterations in urine elimination Some insight has been gained into the intrarenal mechanisms which by their exquisite sensibility confer upon the kidney the power to adjust with nicety its excretory accomplishment to the excretory demands of the organism which it serves

The author s interest and the information which has grown out of it procee led from a single ob ervation made in collaboration with O H Plant in 1916 reported before the American Physiological Society in that year but not published in full until 1922[24] A rabbit s kidney was perfused with his own blood under circumstances which insured constant rate of blood flow regardless of changes in the caliber of the renal bloodvessels When the renal bloodvessels were constricted either by stimulation of the vaso-

with the rise in renal b'
was a swelling of the ki
taneous vaso lilatation
such as the leg or gut

phenomenon, it was quite clear that the result must have been due to the peculiar arrangement of the bloodvessels in or connected with the Malpighian bodies In the belief that the efferent vessel was equipped both with muscle fibers and with constrictor nerves, the swelling was explained as the result of constriction of the efferent vessel with consequent distention of the glomerular capillaries proximal to it

This result constituted the first experimental evidence of which the author is aware in the support of the thought expressed long before by Ludwig, later by Starling and which must have been in the minds of many of those who believed in the filtration doctrine, namely that intraglomerular pressure is susceptible of regulation by changes in the relationship of the caliber of the afferent and efferent vessels

It was for the purpose of advancing the study of this problem further that we first turned to the kidney of the frog hoping that it might be possible to gain direct microscopic visualization of the changes inferred to take place in the rabbit s kidney The possibility of microscopic study of the frog s glomeruli was successfully realized [27] and when minute doses of adrenalin were injected into the frog s circulation, it was found by actual measurement that the glomerular tufts increased in size This was taken to indicate that constriction of the efferent vessel of the glomerulus induced by

pressure under precisely similar conditions and found that minute dosage with adrenalin caused it to increase His results, therefore, upheld the original conclusion In one experiment, for example adrenalin caused glomerular capillary pressure to rise from 12 to 21 cm H_2O, while aortic pressure changed only from 37 to 40 cm

Finally an experiment was developed in which the essential elements of the original experiment on the rabbit's kidney were reproduced in the frog with the added item of photography of the glomeruli [28] The frog s kidney was arranged for perfusion with

it had caused constriction of some part of the vascular system of the kidney At the same time there was a visible measurable enlargement of the glomerular capillary tuft This could only have been obtained as a result of increased pressure within the glomerular capillaries which in turn could only have been due to constriction of vessels distal to the glomerular tuft Adrenalin does

not, by direct action, dilate the glomerular capillaries, it did not, as Sollmann has suggested, dilate the afferent vessels, from the work on the rabbit kidney we knew that constriction of the intertubular capillaries was not responsible for distention of the glomerulus, hence we were forced to conclude that adrenalin had constricted the efferent arterioles

This succession of experiments showed that increase of pressure in the renal circulation causes corresponding increase in urine

During the progress of the work our thoughts centered upon the possibility of preferential action which might be exerted by a substance upon the efferent as contrasted with the afferent arteriole If such could be demonstrated we should be able to understand

developed was as follows It is common belief that the efferent vessel is smaller in diameter than the afferent if this is so, and if a constrictor agency (chemical or otherwise) acted equally upon both, resistance to blood flow would increase in the smaller (efferent) vessel more than in the larger (afferent), and if intensity of effect on both vessels were not too great might actually increase glomerular capillary pressure Thus it was reasoned that if a constrictor substance like adrenalin were present in the renal blood stream in *minimal* effective concentration, the only increase in resistance to blood flow would be produced in the efferent vessels, this would lessen the rate of blood flow through the kidney, but at the same time would heighten glomerular capillary pressure and hence increase glomerular urine formation Experiments were made to test the soundness of this reasoning, first by Plant and the author,[26] later by Mendenhall,[17] and by Livingston [13] The rabbits were eviscerated to stabilize their renal circulation and arranged to record changes in size of the kidney rate of blood flow through the kidney and rate of urine flow In a few experiments with

seemed to show that such a preferential constrictor action on the efferent vessel had been produced, but the number of experiments in which it could actually be demonstrated was too small to be thoroughly convincing

Another direction which this thought of possible preferential action of substances upon the afferent vessel took was inconsistent with the first like the first supposition this latter one has as yet yielded inconclusive experiments but the author is inclined to think it gives prospect of greater fruitfulness if further explored It concerns the action of substances which dilate the renal blood vessels and produce diuresis

Pharmacologists have thought for many years that the action of chemical agents upon living tissue could be decreased by the presence of colloid material (demulcent action) Whatever theory is held concerning the nature of glomerular function we may regard it as established that a protein free fluid is separated from the blood in its passage through the glomerular capillaries This must mean that the concentration of plasma proteins in the blood which flows through the efferent vessels is higher than the concentration of the plasma proteins of the blood which flows through the afferent vessels Hence if the water of the plasma of the renal blood stream contains a substance in solution which relaxes arterial muscle and if our conception of the demulcent action of colloids is correct it could be supposed that the dilator action of the substance would be greater upon the muscle of the afferent vessels than upon that of the efferent because of the lower con centration of colloids in the blood entering the glomerulus A few years ago the author made a group of experiments which seemed to give experimental evidence of the truth of this hypothesis The frog s kidneys were perfused with acacia solutions of two concen trations 3 and 6 per cent To a portion of each of these was added caffeine 0 1 per cent The dilator action of caffein in the weaker solution was greater than its dilator action in the stronger acacia solution The details of these experiments were never published

n In perfusing the kidneys

that following the action

ial perfusion rate was not

restored hence the control level of vascular tone was not the same in the two tests which were compared in each experiment This was pointed out by Dr H Florey who then proceeded to repeat the experiments on the kidney and to extend them to the systemic vessels as well in the belief that if the thought was correct it *should be demonstrable in any set of* bloodvessels which caffeine was capable of dilating He failed to substantiate the author s earlier results encountering the same difficulty which he had encountered in the restoration of the original vascular tone be tween the testing of the two solutions With Dr J A Reisinger the author submitted the question to reexamination Encouraged by the observations of Krogh and of Drinker that normal serum contains a substance or substances which have the power of preserv

ing the normal tone and the permeability of perfused vessels, and and guided particularly by Drinker s work solutions were prepared each of which contained 5 per cent of sterile normal horse serum

solution caused perfusion flow to increase to a greater extent and more promptly than when dissolved in the 5 per cent acacia

Possibly it is unwise to call attention to such experiments as these before they have been pushed to a completely satisfying conclusion It is hoped to do this soon In the meantime this

substances which the welfare of the body requires to be excreted at the same time retaining those which it cannot afford to lose we

example with the presence in the blood of excess of *harnfahige* substances is not sufficient to explain the diuresis which rids the blood of such excess If our ingenuity in experiment is sufficient we shall surely find means by which the kidney is able to accomplish this independently of gross change in the renal circulation and among these means we may expect to find delicate adjustments of glomerular pressure

There is another factor involved in maintenance and adjustment of glomerular capillary pressure which is associated with the filtration of cell free protein free fluid from the blood as it flows through the glomerular capillaries viz viscosity The high viscosity of

afferent This must form an element in the resistance to exit of blood from the glomerulus and hence in the glomerular capillary pressure It is an element which must vary with rate of blood flow volume of glomerular filtrate and caliber of vessels and these

are not so sure of this but even if the two vessels are of the same caliber the higher viscosity of blood in the efferent vessel must inevitably produce the same effect as would smaller caliber

2 **Rate of Blood Flow Through the Kidney** —If filtration is the sole process of glomerular separation of fluid from the blood glomerular blood pressure must be the prime physical factor upon which it depends Renewal of blood however in contact with the filtration surface is essential if filtration is to continue Since all or nearly all of the renal blood passes through glomerular capillaries the rate of renal blood flow is an expression of rate of renewal of fluid in the filter Because the colloids of the blood do not pass through the filter the first fluid to be filtered from any portion of blood encounters the least osmotic resistance to its filtration Each particle of filtrate subsequently formed from that portion encounters greater and greater resistance because of the increasing concentration of non filterable colloids left behind Stagnation of blood in glomerular capillaries is therefore an impediment rapid flow of blood an aid to the glomerular filtration process

Despite the probability indicated in the previous section that changes in caliber of the efferent vessel may effect changes in

same direction When by heightened aortic pressure alone or by dilatation of the renal vessels with maintained aortic pressure the glomerular pressure rises the blood flow increases when by decrease of aortic pressure or by constriction of renal vessels glomerular pressure falls so also does glomerular blood flow Thus alterations in renal blood flow can commonly be regarded as intensifying the effect of changes in renal blood pressure

These statements are all inferences No studies have yet been made in which renal blood pressure has been kept constant in order to study the uncomplicated effects of alterations in renal blood flow Many experiments have been made in which renal blood flow was measured along with arterial pressure and rate of urine formation While they have shown that widely different rates of urine formation may be associated with the same rate of blood flow they do not permit us to identify with clarity the share which change in blood flow takes in the production of changes in renal function as a whole much less of any one of its constituent factors

It will be recalled that one reason for Heidenhain s denial of the validity of the filtration hypothesis was derived from the fact that partial obstruction of the renal vein did not increase urine output Arguing that such obstruction must increase glomerular capillary pressure he concluded that pressure is not a primary factor in glomerular funct on but is important only insofar as it is necessary for an adequate blood flow He conceived the glomerular epithelium to be a secretory structure the functional capacity of which depends upon its state of nutrition this in turn be ng dependent

upon rapidity of blood flow through the capillaries We now believe that Heidenhain was wrong if conditions are created in which partial obstruction of the renal vein does not impede blood flow urine is not decreased it is increased In Heidenhain s experiments in addition to the mechanical effects produced by

that the nutrition of the glomerular membrane is dependent upon the rate of blood flow through it is one which it is wise to keep in mind While we conceive of the membrane as one through which the physical process of filtration occurs it must be remembered that it is a living membrane and that its properties must vary with the state of vitality of its cells Data on the relation between changes in its vitality and its properties of permeability are not at hand

3 **Permeability of the Glomerular Membrane** On the question of changes in permeability of the glomerular membrane as factors in the regulation of normal glomerular function the author has no positive information to offer It may be recalled that brief interruption of the renal circulation causes albumin to appear in the

and Shevky increased glomerular permeability to trypan blue[20] Attempts have been made to explain in part the diuretic action of caffeine by an effect on glomerular membrane permeability It was found that diuresis from caffeine outlasts its apparent power to dilate renal vessels and hence it was argued that the effect could not be ascribed to vascular action and since evidence that it lessens reabsorption from the tubules is uncertain recourse was taken to the conception of increased permeability

The difficulties which stand in the way of actual determinations of the rate of glomerular filtration under constant conditions of blood pressure and blood flow are apparently insuperable Until such determinations have been made however the explanations of diuretic and antidiuretic effects by changes in glomerular permeability however plausible will contain unsatisfactory elements of uncertainty

4 **Extent of Filtration Surfaces** —Early in the course of the work which Dr C F Schmidt and the author began in 1920 on the glomerular circulation in living frogs they were struck by the different appearances which different glomeruli presented[27] One glomerular tuft might show many capillary channels through all of which blood was swiftly flowing another might seem to consist of only one or two capillary loops through which blood flow was

apt to be sluggish In some instances one-half of the glomerular tuft appeared constricted and empty of blood the other dilated and filled with blood Such differences very puzzling at first soon came to be expected and they came to believe that what was being seen represented different physiological states of the glomerular circulation

At about the same time it was discovered that the number of visible glomeruli in a microscopic field through which blood was flowing at any one moment was variable By subjecting the kidney to vasoconstrictor influences the number of active glomeruli could be reduced at will likewise by introducing renal vasodilators the number of active glomeruli could be increased

A third phenomenon was observed in some of the very first successful experiments which were made vi that blood flow through a glomerulus or a group of glomeruli or even through a capillary loop of a single glomerulus was apt to exhibit irregular variation in its velocity which amounted in many cases to definite intermittence of flow

This observation of intermittence has been repeated so many times since by so many different persons in the author s laboratory that despite the failure of Tamura[31] and his collaborators to see it *in Japanese frogs the author still has faith in the correctness of* the observation Dr H Okkels of Copenhagen has written that he has observed it in the frogs which he has studied

These observations led to the inference that not all of the glo

that the extent of functioning glomerular capillary surface is nor mally a variable that constriction of renal vessels other things being equal not only lessens glomerular blood pressure and rate *of glomerular blood flow* but also the extent of glomerular mem brane surface accessible to the blood renal vasodilatation on the other hand not only increases glomerular pressure and rate of renewal of blood in contact with glomerular membrane but also increases the accessible glomerular area

The inclusion of this factor as a physiological means of regulating the degree of glomerular function made it easier to understand how

slight changes in the composition of the blood might cause relatively great change in volume of urine formed

Evidence that this mode of regulation of glomerular function exists in the mammalian kidney was later supplied by Khanolkar,[10] and by Hayman and Starr [7] [illegible] the circulation of rabbits, exc[illegible] water, and in frozen sections [illegible] whi[illegible] inje[illegible] timated the number of [illegible] e dye By injecting adrenalin or caffeine they were able to vary at will the number of glomeruli through which blood was flowing at any one moment from 5 to 100 per cent of the total

If the conclusion to which these experiments led is correct, an important question arises how the units which do not receive blood escape asphyxial damage It is well known that interruption of the renal circulation for very short periods is followed by transient albuminuria, attributable to glomerular damage The answer which Schmidt and the author made to the question was derived from their observations on intermittence It seemed right to assume that when only a fraction of the total number of glomeruli are being supplied with blood at one time, the individuals which make up this fraction are constantly changing so that no one is deprived of circulation long enough to suffer damage Langley s work[12] on the small vessels of the frog s web suggested and gave confidence in this view, for he showed that repeated stimulations of the sciatic nerve cause different vessels to respond by constriction Following Langley's thought, it seemed credible that when a vessel closed because of a constrictor stimulus, influences such as asphyxia of its muscle began to develop which would tend to cause it to relax, and, having relaxed, it would for a time be refractory to the continuing constrictor stimulus

It must be pointed out that when the capillaries in a single glomerular tuft exhibit alternations in blood flow of the sort described, these are not due to constriction of the capillary loops They are due either to contraction of the origin of the capillary from the afferent vessel or to contraction of the afferent vessel at the point of its branching from its parent artery or of a similar branching proximal to this Conclusive proof of the first type of capillary glomerular intermittence was seen in an experiment in which one loop exhibited steady uninterrupted flow, while two other [illegible]

at the origin of the glomerular capillaries from the afferent arteriole Similar behavior at the arterial origin of a capillary was described by Tarchanoff and by Landis, and Okkels, having confirmed the observation of Ruyter[29] that the muscular wall of the afferent arteriole exhibits a specialized thickening close to the glomerulus, found that mechanical stimulation at that point produced contraction [18]

FUNCTIONS OF THE RENAL TUBULE

Reabsorption —There can now be little reasonable doubt of the *existence of processes of reabsorption in the renal tubule* When Wearn,[34] for the first time so far as the author knows punctured the capsule of Bowman and withdrew samples of the fluid which was accumulating there, and when upon appropriate test it was found to contain both sugar and Cl, the urine issuing from the ureter containing none the principle of reabsorption was established Much previous evidence was in existence which had rendered reabsorption justifiably believable but no previous experiment possessed the compelling force of this one

In one of Hill s[9] papers the objection has been raised that the process which was used to collect the glomerular urine was equivalent to cupping that the negative pressure employed to draw the fluid up into the pipette produced suction upon the glomerular membrane and that this resulted in the collection of something quite different from the normal glomerular fluid

that there could be no question of reflux from tubule, and collection of glomerular fluid was made against a positive pressure of 3 to 10 mm Hg Furthermore almost all of the collections which

tubule closed

At about the same time that the experiments by Wearn and the author were being made Bieter and Hirschfelder[7] injected phenol red into frogs and observed that the contents of the tubules appeared to be more intensely red than did the contents of the capsule of Bowman This observation was presented as proof of reabsorption of water from the tubule

There can be no doubt concerning the correctness of this observation, and there is no doubt in the author s mind that water is actually reabsorbed from the tubules but the claim that the observation constitutes proof of water reabsorption seems to beg the disputed question of secretion of phenol red by the tubules

Other evidence on this point is available [22] For example, let a frog s kidney be perfused *via* the renal arteries with a dilute solution

of phenol red in Ringer's fluid long enough to fill the lumina of

diffuse pink to intensely red irregular curved streaks These streaks can be proved to represent accumulations of the dye within the lumina of the tubules much more highly concentrated than the original fluid Such concentration could be produced only by the reabsorption of water

Essentially the same demonstration can be made in a single tubule of the living frog Inject a minute quantity of phenol red solution into the lumen of a tubule by a pipette thrust into the intracapsular space Block the neck of the tubule with a glass rod The injected solution then remains stationary within the tubule and the observer can see that in volume it becomes gradually less while the intensity of its color increases These experiments are important in furnishing objective evidence not only that water is reabsorbed but also that the highly diffusible substance phenol red is not reabsorbed to the same degree *i e* the reabsorption is selective

We have a little information concerning the portions of the tubule in which reabsorption occurs White[39] obtained evidence that the reabsorption of dissolved constituents of the glomerular filtrate takes place in the proximal sections of the tubule He injected red blood cells into the intracapsular space and found that they became invisible in passing through the proximal convolutions This he attributed to the reabsorption of chloride to such a degree that hemolysis occurred

By filling a single tubule with phenol red and then blocking it at different points to learn where the concentration of color became most conspicuous the author has found that reabsorption of water takes place in an intermediate part of the tubule distal to the proximal convolutions And if we may regard reabsorption of hydroxyl ions as the cause of the acidity of urine it can be stated that this occurs in the distal convolutions because phenol red does not turn yellow within the tubule until it reaches the distal convolutions As yet however there is no direct proof that urinary acidity in the frog is produced by reabsorption of OH+

These statements are the only ones which the author can make concerning differentiation of reabsorptive function among different parts of the renal tubule *

*

occurs only in the distal tubule Water is reabsorbed from both sections of the tubule more from the distal than from the proximal

Concerning the nature of the process of reabsorption we have no information other than that it is not to be explained, as Ludwig first conceived by simple diffusion It must be regarded as active and selective In experiments on the surviving frog's kidney in which the tubules and the intertubular capillaries are filled with the same solution (Ringer s) chloride and sugar pass from the interior to the exterior of the tubule phenol red does not The selective reabsorption thus demonstrated and the selective impermeability as well are dependent upon the vitality of the cells of *the tubule, for they are not demonstrable* in the kidney poisoned with $HgCl_2$ or damaged by long perfusion It is proper to think of the reabsorption processes concerned as ' secretory " for certainly the activity of cells is a necessary factor in it

We have scarcely *the beginning of knowledge of the factors* which control reabsorption from the renal tubule Clark[3] has shown that the concentration of glucose in the fluid which bathes the tubules determines the elimination of glucose *via* the ureter C J Gamble has found that increase in concentration of Cl in the fluid used to perfuse the renal portal vein stops the reabsorption of Cl from the tubules Hence we may conclude that the level of concentration of certain urinary constituents in the blood in the intertubular capillaries controls the reabsorption of those substances from the urinary tubule A M Walker showed in perfusion experiments that changes in rapidity of flow of the glomerular filtrate through the tubules may greatly modify the Cl content of the fluid issuing from the ureter Hence time of contact of glomerular fluid with the tubular epithelium may be looked upon as a controlling factor Continued search for other controlling factors, nervous and chemical, will surely bring to light more subtle mechanisms than those by which reabsorptive power of renal epithelium *is adjusted to the needs of the body*

Secretion —Neither the space nor the knowledge at the author's disposal is sufficient to justify an attempt at thorough discussion of the highly involved question of secretion by the renal tubule Four groups of experiments will be described to indicate the more [illegible] representative attempts in which the author has taken part to [illegible] of view derived from them. [illegible] important paper published by Marshall and Vickers, in [illegible] They discovered that when phenol red (phenolsulphonephthalein) is injected into dogs, *by far* the greater part of the injected dye quickly accumulates in the cells of the convoluted portions of the renal tubules Then, from estimations of the amount of phenol red eliminated by the kidney *in measured time* and the concentration of 'free" or filterable phenol red in the blood plasma, they computed that the quantity of dye eliminated was greater than the quantity of filterable dye

which had traversed the kidney in the blood stream during that interval The excess dye eliminated they believed to have been secreted from the deposit previously laid down in tubule cells Their argument contained two unproved assumptions one that the glomerular fluid contains phenol red in concentration identical with that of an ultrafiltrate from the plasma From later work on frogs kidneys we believe this assumption to be correct The other was that maximal rate of blood flow through the dog s kidney cannot be greater than 5 cc per gram per hour Thus we believe

kidney *

The outcome of the interest which this paper by Marshall and Vickers aroused was a collaborative effort by Barnwell and the
which should
at the same
t of our effort
was an exceedingly simple experiment easily performed which seemed to yield *prima facie* evidence of the existence of secretion of phenol red by tubules The living kidney of a pithed frog was excised the blood washed out of it by perfusing a little of Ringer s solution through its vessels and then it was immersed in a beaker of thoroughly oxygenated Ringer s solution containing a low concentration of phenol red (0 01 to 0 03 per cent) During the following three to five hours it was taken out of the solution at intervals and examined microscopically After one half hour and to an increasing degree thereafter the lumina of some of the loops of tubules visible on inspection of the ventral surface were found to be filled with fluid far more intensely colored than was the solution in which the kidney was immersed Obviously the dye had penetrated into the tubules and was concentrated there equally obviously the glomeruli could not have participated in the process for no fluid at all had passed through their vessels the most obvious conclusion was that tubule cells had secreted the dye from the surrounding fluid into their lumina Further elaboration of the experiment however yielded observations which forced us to think that quite a different explanation was credible

(a) When the experiment was repeated after the addition of a little HCN to the phenol red solution in which the kidney was immersed no accumulation of the *concentrated* dye in the tubules occurred but it was easily seen that the dye in low concentration

* Further experiments by Marshall (Am J Physiol 99 77 1931–32) have established the conclusion drawn by Marshall and Vickers that in dogs glomerular filtration alone is inadequate to account for the rate of excretion of phenol red

had penetrated into the tubules The conclusion was drawn that the vital factor in the original experiment was not the passage of the dye from the outside to the inside of the tubule but rather its concentration within the tubule

(b) The tubules of a freshly excised kidney were filled with phenol red solution by injection *via* the ureter this was tied to prevent leakage of the injected fluid and the kidney immersed in oxygenated Ringer s solution containing no dye Immediately after the injection the whole kidney was uniformly pink *but after* immersion for one hour the dye became localized in precisely similar fashion to that seen in the original experiment *i e* in some of the parts of the tubules visible from the ventral aspect there were accumulations of concentrated dye these being interspersed among areas of relatively little color When this experiment was repeated with the addition of HCN to the injected dye solution no such localized concentrations of dye occurred On the contrary the *kidney diffusely colored gradually gave up the dye to the fluid* in which it was immersed

From these experiments it is obvious that the fluid with which the tubule of the normal kidney was filled had been set in motion and that at one portion of the tubule water but not phenol red had been extruded (reabsorbed) so that presently that part of the tubule came to contain concentrated dye other parts at the same time becoming relatively empty of dye The tubule of the HCN kidney on the other hand had lost both its power of extruding water and of retaining phenol red

(c) Experiments similar to those of the second group just described were made with the colloidal non-diffusible dye vital red The results were the same except that in the HCN kidney the dye did not leach out into the surrounding fluid but remained for hours diffusely distributed throughout the kidney

The conclusions which were drawn from this succession of tests were these When the excised surviving kidney is immersed in oxygenated Ringer s fluid containing phenol red the fluid slowly passes through the wall of the tubule into its lumen as the result of a process which is not inhibited by HCN and hence can be thought of as diffusion rather than secretion at the same time reabsorption processes are operating to extrude water but not phenol red from a portion of the tubule situated distal to the proximal convolutions (This is the portion most easily seen from *the ventral surface*) Both the water extruding and phenol red retaining capacities of this part of the tubule are inhibited by HCN and hence are vital in nature The simultaneous occurrence of inward diffusion of dilute dye outward extrusion of water and retention of dye within the lumen of the extruding portion results in the accumulation of highly concentrated dye in that portion

If our reasoning is sound, it is apparent that our original experiment with the excised kidney, which seemed to provide objective evidence of tubular secretion of phenol red, finds a more acceptable explanation in processes of non-selective diffusion into the tubule and selective, active extrusion from the tubule *

These results are not to be regarded as confirming or not confirming the conclusions which Marshall and Vickers drew from their experiments They may have value in that they call attention to the possibility that diffusion from blood or lymph into renal tubules may play a part in excretion by the kidney We have no reason to think it important in the frog's kidney, it is conceivable that it may be a factor of moment in the mammalian kidney, the tubules of which elaborate a fluid highly hypertonic to blood But methods of studying the question in mammals are not now obvious

2 The second group of experiments which the author wishes to describe under the general heading of secretion by the renal tubule was the direct outcome of the estimations made by Walker and the author of the concentration of phenol red in glomerular fluid collected while the kidney was excreting that dye They are analogous to those by Marshall and Vickers described above

If we know the concentration of some chosen dissolved constituent in the glomerular filtrate the total number of glomeruli participating in the process of filtration and the total amount of the constituent excreted by the kidney in a measured time, it is obvious that we can compute an average for the rate at which filtration must have proceeded in each glomerulus during that time in order to have effected the clearance from the blood of the amount of the constituent which was actually excreted In the frog we know [illegible]

the basis of an opinion concerning the adequacy of glomerular filtration to clear the blood of the amount of the chosen constituent which was actually eliminated and hence, also, of the necessity of postulating secretory functions for the renal tubule

Walker and the author have made a series of 32 experiments on frogs in which this type of computation of the average rate of glomerular filtration has been made Phenol red was the constituent of glomerular fluid chosen for study because of the ease with which its concentration in minute amounts of fluid can be determined The details of one experiment will suffice to illustrate the entire group

Three milligrams of phenol red were injected subcutaneously

* Holton and Bensley (Am J Anat 47 341 1931) object strongly to this interpretation and the experiments of Hober and Meirowsky (Pfluger's Arch f d ges Physiol 230 331 1932) appear to controvert it

had penetrated into the tubules The conclusion was drawn that the vital factor in the original experiment was not the passage of the dye from the outside to the inside of the tubule but rather its concentration within the tubule

(*b*) The tubules of a freshly excised kidney were filled with phenol red solution by injection *via* the ureter this was tied to prevent leakage of the injected fluid and the kidney immersed in oxygenated Ringer s solution containing no dye Immediately after the injection the whole kidney was uniformly pink but after *immersion for one hour the dye became localized in precisely similar* fashion to that seen in the original experiment *i e* in some of the parts of the tubules visible from the ventral aspect there were accumulations of concentrated dye these being interspersed among areas of relatively little color When this experiment was repeated with the addition of HCN to the injected dye solution no such localized concentrations of dye occurred On the contrary the kidney diffusely colored gradually gave up the dye to the fluid in which it was immersed

From these experiments it is obvious that the fluid with which the tubule of the normal kidney was filled had been set in motion and that at one portion of the tubule water but not phenol red had been extruded (reabsorbed) so that presently that part of the tubule came to contain concentrated dye other parts at the same time becoming relatively empty of dye The tubule of the HCN kidney *on the other hand had lost both its power of extruding* water and of retaining phenol red

(*c*) Experiments similar to those of the second group just described were made with the colloidal non-diffusible dye vital red The results were the same except that in the HCN kidney

but remained

ssion of tests

were these When the excised surviving kidney is immersed in oxygenated Ringer s fluid containing phenol red the fluid slowly passes through the wall of the tubule into its lumen as the result of a process which is not inhibited by HCN and hence can be thought of as diffusion rather than secretion at the same time reabsorption processes are operating to extrude water but not phenol red from a portion of the tubule situated distal to the proximal convolutions (This is the portion most easily seen from the ventral surface) Both the water-extruding and phenol red retaining capacities of this part of the tubule are inhibited by HCN and hence are vital in nature The simultaneous occurrence of inward diffusion of dilute dye outward extrusion of water and retention of dye within the lumen of the extruding portion results in the accumulation of highly concentrated dye in that portion

If our reasoning is sound it is apparent that our original experiment with the excised kidney which seemed to provide objective evidence of tubular secretion of phenol red finds a more acceptable explanation in processes of non selective diffusion into the tubule and selective active extrusion from the tubule *

These results are not to be regarded as confirming or not confirming the conclusions which Marshall and Vickers drew from their experiments They may have value in that they call attention to the possibility that diffusion from blood or lymph into renal tubules may play a part in excretion by the kidney We have no reason to think it important in the frog s kidney it is conceivable that it may be a factor of moment in the mammalian kidney the tubules of which elaborate a fluid highly hypertonic to blood But

the author of the concentration of phenol red in glomerular fluid collected while the kidney was excreting that dye They are analogous to those by Marshall and Vickers described above

If we know the concentration of some chosen dissolved constituent in the glomerular filtrate the total number of glomeruli participating in the process of filtration and the total amount of the constituent excreted by the kidney in a measured time it is obvious that we can compute an average for the rate at which filtration must have proceeded in each glomerulus during that time in order to have effected the clearance from the blood of the amount of the constituent which was actually excreted In the frog we know from many collections of glomerular fluid what the order of magnitude of the rate of glomerular filtration actually is By comparing computed with known rates of glomerular filtration we can form the basis of an opinion concerning the adequacy of glomerular filtration to clear the blood of the amount of the chosen constituent which was actually eliminated and hence also of the necessity of postulating secretory functions for the renal tubule

Walker and the author have made a series of 32 experiments on frogs in which this type of computation of the average rate of glomerular filtration has been made Phenol red was the constituent of glomerular fluid chosen for study because of the ease with which its concentration in minute amounts of fluid can be determined The details of one experiment will suffice to illustrate the entire group

Three milligrams of phenol red were injected subcutaneously

* Holton and Bensley (Am J Anat 47 241 1931) ob ect strongly to th s interpretat on and the experiments of Hober and Me rowsky (Pfluger s Arch f d ges Phys ol 230 331 1932 appear to contro ert it

had penetrated into the tubules The conclusion was drawn that the vital factor in the original experiment was not the passage of the dye from the outside to the inside of the tubule but rather its *concentration within the tubule*

(*b*) The tubules of a freshly excised kidney were filled with phenol red solution by injection *via* the ureter this was tied to prevent leakage of the injected fluid and the kidney immersed in oxygenated Ringer s solution containing no dye Immediately after the injection the whole kidney was uniformly pink but after immersion for one hour the dye became localized in precisely similar fashion to that seen in the original experiment *i e* in some of the parts of the tubules visible from the ventral aspect there were accumulations of concentrated dye these being interspersed among areas of relatively little color When this experiment was repeated with the addition of HCN to the injected dye solution no such localized concentrations of dye occurred On the contrary the kidney diffusely colored gradually gave up the dye to the fluid *in which it was immersed*

From these experiments it is obvious that the fluid with which the tubule of the normal kidney was filled had been set in motion and that at one portion of the tubule water but not phenol red had been extruded (reabsorbed) so that presently that part of the tubule came to contain concentrated dye other parts at the same time becoming relatively empty of dye The tubule of the HCN kidney on the other hand had lost both its power of extruding water and of retaining phenol red

(*c*) Experiments similar to those of the second group just described were made with the colloidal non-diffusible dye vital red The results were the same except that in the HCN kidney the dye did not leach out into the surrounding fluid but remained for hours diffusely distributed throughout the kidney

The conclusions which were drawn from this succession of tests were these When the excised surviving kidney is immersed in oxygenated Ringer s fluid containing phenol red the fluid slowly passes through the wall of the tubule into its lumen as the result of a process which is not inhibited by HCN and hence can be thought of as diffusion rather than secretion at the same time reabsorption processes are operating to extrude water but not phenol red from a portion of the tubule situated distal to the proximal convolutions (This is the portion most easily seen from the ventral surface) Both the water-extruding and phenol red retaining capacities of this part of the tubule are inhibited by HCN and hence are vital in nature The simultaneous occurrence of inward diffusion of dilute dye outward extrusion of water and retention of dye within the lumen of the extruding portion results in the accumulation of highly concentrated dye in that portion

If our reasoning is sound it is apparent that our original experiment with the excised kidney which seemed to provide objective evidence of tubular secretion of phenol red finds a more acceptable explanation in processes of non selective diffusion into the tubule and selective active extrusion from the tubule *

These results are not to be regarded as confirming or not confirming the conclusions which Marshall and Vickers drew from their experiments They may have value in that they call attention to the possibility that diffusion from blood or lymph into renal tubules may play a part in excretion by the kidney We have no reason to think it important in the frog's kidney it is conceivable that it may be a factor of moment in the mammalian kidney the tubules of which elaborate a fluid highly hypertonic to blood But methods of studying the question in mammals are not now obvious

2 The second group of experiments which the author wishes to describe under the general heading of secretion by the renal tubule was the direct outcome of the estimations made by Walker and the author of the concentration of phenol red in glomerular fluid collected while the kidney was excreting that dye They are analogous to those by Marshall and Vickers described above

If we know the concentration of some chosen dissolved constituent in the glomerular filtrate the total number of glomeruli participating in the process of filtration and the total amount of the constituent excreted by the kidney in a measured time it is obvious that we can compute an average for the rate at which filtration must have proceeded in each glomerulus during that time in order to have effected the clearance from the blood of the amount of the constituent which was actually excreted In the frog we know

of magni-

comparing

can form

the basis of an opinion concerning the adequacy of glomerular filtration to clear the blood of the amount of the chosen constituent which was actually eliminated and hence also of the necessity of postulating secretory functions for the renal tubule

Walker and the author have made a series of 32 experiments on frogs in which this type of computation of the average rate of glomerular filtration has been made Phenol red was the constituent of glomerular fluid chosen for study because of the ease with which its concentration in minute amounts of fluid can be determined The details of one experiment will suffice to illustrate the entire group

Three milligrams of phenol red were injected subcutaneously

* Holton and Bensley (Am J Anat 47 241 1931) object strongly to this interpretation and the experiments of Hober and Mezrowsky (Pflüger's Arch f d ges Physiol 230 331 193) appear to controvert it

into a large frog (*Pipiens*) Salt solution was also injected at the beginning of the experiment in order to insure diuresis and active circulation through all the glomeruli Urine collected from one kidney for thirty minutes measured 0 1 cc and contained 0 1 mg of phenol red The average concentration of phenol red in the blood plasma during the one-half hour was 9 mg per 100 cc An ultrafiltrate from the plasma was estimated (on the basis of many actual filtrations of frogs plasma containing phenol red) to contain approximately 7 5 mg phenol red per 100 cc The number of glomeruli in the kidney was 1954 From these figures assuming that all of the phenol red was eliminated by the glomeruli the average rate of filtration in each glomerulus must have been 1 36 c mm per hour

Of the 32 estimations of which the above experiment is one the two highest computed rates of average glomerular elimination were 2 1 and 2 3 c mm per glomerulus per hour in 16 the figure was less than 1 in 8 between 1 and 1 5 in 6 between 1 5 and 2

hour The conclusion drawn from these experiments is that they yield no evidence that the process of glomerular filtration alone ... for all of the elimination

n to the results of some of his experiments in which the urea content of urine from the ureter were determined The conclusion was similar ... that glomerular function is adequate to account for the urea clearance from the blood

3 The experiments next to be described related to the behavior of another dye in the kidney viz neutral red and were made in collaboration with Dr J A Reisinger In a paper from Hober s laboratory Scheminsky[30] published results which seemed to show that this substance is eliminated mainly by the tubules little if at all by the glomeruli He subjected frogs kidneys to perfusion both through the renal arteries and through the renal portal vein Addition of neutral red to the arterial fluid resulted in the elimination of a small amount of the dye the concentration in the urine being less than that in the perfusion fluid Addition to the renal portal perfusion fluid on the other hand was followed by the appearance of the dye in the urine in concentration three to five times greater than that of the perfusion fluid

Shortly after this Oliver and Shevky[9] and MacKay and Oliver[14] published the results of experiments which confirmed Scheminsky s conclusion and in a very convincing way demon

strated a profound difference in the mode of excretion of neutral red and phenol red

Neutral red differs from phenol red in being less diffusible, less absorbable, more toxic and having distinctly less tinctorial power Even when given by intravenous injection it is difficult to establish a plasma concentration as high as 5 mg per 100 cc When a solution of neutral red is mixed with frogs plasma, and the mixture filtered through collodion or cellophane, the protein-free filtrate contains less than one-tenth of the original concentration of dye, between 90 and 95 per cent are adsorbed by the plasma proteins

Neutral [illegible]
branes [illegible]
perfused [illegible]
tral red [illegible]
the perfusion was found to contain the same concentration of the dye

In a similar experiment the perfusion fluid consisted of sterile horse serum, diluted with equal volume of Ringer s solution, neutral red being added to make 0 005 per cent In this case the collected glomerular fluid showed a concentration of only 0 0004 per cent neutral red *i e*, the concentration which would have been expected in a fluid obtained with collodion or cellophane

When living frogs were injected with neutral red and collections of glomerular fluid made it was rarely possible to see any color in them This does not necessarily mean that none of the dye was present, for the tinctorial power of neutral red is so low that in the capillary tubes which we used for color estimations, no red tint could be seen in concentrations less than 0 0005 to 0 00025 per cent The essential details of 1 experiment typical of a number of others are as follows

March 19 1930 R pipiens ♀ about 60 gm [illegible]

[illegible] per cent
[illegible] per cent
[illegible] per cent
[illegible] per cent
[illegible] per cent
[illegible] per cent

[illegible]

from the experiments with phenol red

In the seventeen minutes from 4 30 to 4 47 P M 0 037 mg of neutral red was excreted The volume of glomerular fluid, con-

taining less than 0 0005 per cent, which could have contained this amount of neutral red was more than 11 4 cc Assuming the number of glomeruli which were functioning to have been 2000, the average rate for each must have been more than 20 c mm per hour The highest figure for rate of glomerular fluid collection which has ever been estimated in our laboratory is 3 5 c mm. per hour The author finds it exceedingly difficult to believe that a rate of 20 c mm per glomerulus per hour is ever attained under the conditions of our experiments

In another experiment the computed average rate of filtration for each glomerulus was 31 c mm per hour, in still another, 57 c mm per hour

From these experiments on neutral red we have been forced to the same conclusion as that reached by Marshall and Vickers, in 1924, from their experiments with phenol red *viz*, that here is a substance the excretion of which cannot be accounted for by glomerular filtration *Because of the relative non-diffusibility of neutral red the* [illegible]

of the theory of secretion by the renal tubule Schemınsky and Hober believe that the proximal convolutions are the part in which this secretion takes place

These sentences are written with some misgivings Certainly until recently the evidence which has been adduced as proof of the existence of secretion has not possessed convincing power, on the other hand, the basis for sound belief in glomeruler filtration and in active reabsorption from the tubule has been greatly strengthened We have yet to learn whether, in the transfer of such a substance as neutral red from the outside to the inside of the tubule, vitality is actively and directly or passively and indirectly concerned, and we have yet to learn whether normal constituents *of the urine are eliminated from the blood in the same fashion* We [illegible]

conclusions to the physiology of a tubule which originates from a glomerulus cannot yet be made with confidence

Efforts by Reisinger and the author to come closer to direct evidence of the secretion of neutral red by the tubules have thus far failed For example, the excised kidney experiment described on page 41, which is successful with phenol red, failed completely [illegible]

in such experiments salt solution is forced through the tubule from ureter to Bowman's capsule with neutral red no color or only the faintest tinge is seen in the fluid taken from the capsule while with phenol red the color is intense The author has watched the granules of neutral red which appeared to be within tubule cells hoping to see movement or change of size or shape but without success It seems proper to mention these unsuccessful incomplete and apparently paradoxical observations for the sake of emphasizing how little we know of the processes responsible for the passage of material through the wall of the tubule in either direction

4 Finally we have a group of experiments to which the author wishes to make allusion though they are still incomplete for the reason that they possess a trace at least of clinical interest They concern the behavior of the glomeruli and the tubules of the frog during subacute poisoning with $HgCl_2$ A dose of 0 3 mg of this substance in a large frog commonly causes edema and lessened urine output Examination of the living kidney of such a frog at any time between the first and the seventh day of the poisoning reveals the fact that the glomerular circulation is intensely active in all of the glomeruli which can be seen Collection of glomerular fluid can be accomplished at rates wholly comparable with normal frogs But if phenol red is introduced into the tubule of such kidney it does not as in the normal remain within it to become concentrated there by reabsorption of water it diffuses quickly out of the tubule into the intertubular spaces In experiments specifically designed to test the question it also appears that the power of active reabsorption of water from the tubule is lost Hence it appears that the damage which $HgCl_2$ exerts on renal tubules is precisely similar in its physiological consequences to that which HCN was found to produce Loss of power of active reabsorption (of water and substances which are normally reabsorbed) and loss of power of selective retention (of phenol red and substances which are normally retained within the tubule for excretion) The decrease in the formation of urine by such a kidney is obviously not due to suppression of glomerular function It may be due to a non selective diffusion of tubule contents back into the blood stream resulting from the osmotic drawing power of blood plasma proteins together with the abolition by the poison of the normal selective impermeability of the tubule wall

References

1 Bayliss, L E and Walker, A M 1930 The electrical conductivity of glomerular urine from the frog and from Necturus J Biol Chem 87 523 540

2 Bieter R N and Hirschfelder, A D 1924 The excretion of dyes and other substances in the frog's kidney and its bearing upon the theories of renal excretion Am J Physiol 68 326–337

3 CLARK, G A 1922 Glucose absorption in the renal tubules of the frog, J Physiol, 56, 201–205

8 HILL, L, AND MCQUEEN, J M 1921 The measurement of capillary blood pressure in man, Brit J Exp Path, 2, 1–7
9 ———— 1928 The principles of capillary blood pressure measurements as applied to glomerular and tubular function in the kidney, Brit J Exp Path, 9, 127 135
10 KHANOLKAR, V R 1922 Partial activity of the kidney and the "all or nothing principle J Path and Bacteriol, 25, 414–424
11 LANDIS, E M 1926 The capillary pressure in frog mesentery as determined by microinjection methods, Am J Physiol, 75 548–570
12 LANGLEY, J N 1911 The origin and course of the vasomotor fibers of the frog s foot, J Physiol 41, 483–498
13 LIVINGSTON, A E 1928 Further experiments on the effects of small doses of vasoconstrictor substances on the kidney, J Pharm and Exp Therap, 32, 181–188
14 MACKAY, E M, AND OLIVER, J 1930 A comparison of the method of excretion of neutral red and phenol red by the mammalian kidney, J Exp Med, 51, 161 178
15 MARSHALL, E K, JR 1930 A comparison of the function of the glomerular and aglomerular kidney, Am J Physiol, 94 1–10

glomérule renal chez la grenouille, Bull d hist appl physiol et path, 6, 113–118
19 OLIVER, J, AND SHEVKY, E 1929 A comparison of the manner of excretion of neutral red and phenol red by the frog s kidney, J Exp Med, 50 15–29
20 ———— 1930 The relation of particle size to mechanism of dye excretion by the kidney, Am J Physiol, 93, 363–377

nflu-
59,
184–190
26 ———— 1922 The action of minute doses of adrenalin and pituitrin on the kidney, Am J Physiol, 59 191–202

27 Richards A N and Schmidt C F 1924 A lescription of the glomerular circulat on in the frog s kidney and observations concerning the action of adrenalin and various other substances pon it Am J Physiol **71** 178–208
28 Richards A N and Walker A M 1930 Quantitative studies of the glomerular elimnat on of phenol red and indigo-carmine in frogs J Biol Chem **87** 479–498
29 Rutter J H C 1925
afferentia in der Mausemere Ztsc
30 Scheminzky F 1929 I
XVII Mitteilung Die Farbstoff
221 641–691
31 Tamura K Miyamura K Nishina T and Nagasawa H 1927 Studies in the excretion of urine I The glomerular circulation in the living frog s kidney Japan J Med Sci 1 211
32 Walker A M 1930 Comparisons of total molecular concentration of glomerular urine and blood plasma from the frog and from Necturus, J Biol Chem **87** 499 522
33 Walker A M and Elsom K A 1931 A quantitative study of

r

d

89 191 2 0
37 ———— 1929 Observations on the nature of glomerular activity Am J Physiol **90** 689–704
38 White H L and Schmitt F O 1925 Observations on kidney function in Necturus maculosus Science **62** 334
39 ———— 1926 The site of reabsorption in the kidney tubule of Necturus Am J Physiol **76** 483–495

in some of the lower vertebrates except that segment 3 is absent or replaced by a short tubular segment of small diameter and characteristic ciliated epithelium, which has been designated the intermediate segment A ciliated neck segment following the renal corpuscle is also present in many of the lower vertebrates

In Table 2 are collected data on the sizes of the different segments occurring in the renal tubule of vertebrates The measurements are all in millimeters the length being given first in each case the width second blank spaces indicate that the segment does not occur in that kidney The renal tubules of the different classes of vertebrates are presented in Fig 7 in a schematic manner

The data for the table and drawing were obtained as follows For tubule 1 the data of Conel[12] on Bdellostoma and Myxine were used The data for tubule 2 are taken from the observations of Borcea[6] and Nash[49] on the skate (Raia stabulaforis) For tubule 3 the observations of Nash[49] and Defrise[17] on the kidney of the sculpin (Myoxocephalus octodecimspinosus)

* Policard and Mawas [?] describe the nephron of three fresh water teleosts as

TABLE 2.—MEASUREMENTS OF SEGMENTS OF RENAL TUBULE OF VERTEBRATES

Number in figure	Class	Species	Renal corpuscle	Neck segment	Proximal convoluted segment	Intermediate segment	Thin part of Henle's loop	Distal convoluted segment	Initial collecting tubule
1	Cyclostome	Bdellostoma stouti	0.630 × 0.500	0.400 × 0.050	0.75 × 0.350				1.00 × 0.040
2	Elasmobranch	Raia stabuliforis*	0.500 × 0.350	0.050 × 0.040	56.00 × 0.120				0.50 × 0.050
3	Teleost	Myoxocephalus octodecimspinosus	0.125 × 0.100	0.035 × 0.015	6.06 × 0.055				
4	Teleost	Ameiurus nebulosus	0.098 × 0.080	0.108 × 0.025	1.23 × 0.050	0.07 × 0.030		1.13 × 0.035	0.20 × 0.030
5	Teleost	Opsanus tau			4.27 × 0.070				0.47 × 0.070
6	Amphibian	Rana catesbiana	0.125 × 0.100	0.100 × 0.030	3.80 × 0.075	0.20 × 0.022		2.50 × 0.030	0.70 × 0.028
7	Reptile	Chrysemys marginata	0.055 × 0.055	0.025 × 0.020	1.40 × 0.063	0.30 × 0.025		1.00 × 0.038	0.50 × 0.030
8	Bird	Gallus domesticus	0.075 × 0.065		3.60 × 0.063	1.20 × 0.030		2.20 × 0.040	1.00 × 0.038
9	Bird	Gallus domesticus	0.110 × 0.100		7.00 × 0.063		1.70 × 0.018	4.10 × 0.036	1.20 × 0.038
10	Mammal	Lepus cuniculus	0.123 × 0.095		6.90 × 0.036		1.20 × 0.014	5.75 × 0.025	1.00 × 0.020
11	Mammal	Lepus cuniculus	0.133 × 0.102		6.90 × 0.035		12.30 × 0.014	4.35 × 0.025	1.00 × 0.020

* The proximal convoluted segment is intercalated between two other segments which are not represented in other vertebrates. The first of these measured 7.00 × 0.050 and the second 28.00 × 0.050.

not for the ... the tubule As seen in Table 2 the elasmobranch tubule is even longer than a mammalian tubule Its extraordinary length as compared with that of the tubule of other classes has made it impossible to represent it in full in Fig 7

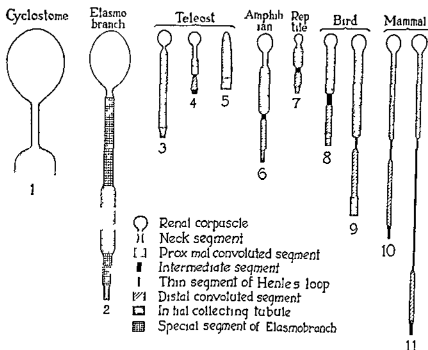


FIG 7 —Schematic representation of nephron of different vertebrates

It is evident that the proximal convoluted segment as judged by the presence of a brush border is the only one occurring in all classes of vertebrates each of the other segments including the

morphological structure offers a method of ascertaining the function of the morphologically distinct parts of the renal unit

Deductions as to Function —Certain deductions as to function are suggested by reviewing the structure of the kidney in this way

suggests a relationship of these cilia to the low blood-pressure of the cold-blooded animals It is probable that in these vertebrates the cilia are needed to aid the relatively low filtration pressure in propelling fluid down the tubule Again, it seems to be reasonably clear that the ability of the kidney to excrete a urine which is

never hypertonic, compared to the blood plasma (for literature, see Smith[62]), in birds, d Errico[21] found that the urine could have a slightly higher osmotic pressure than the plasma and in mammals, as is well known, markedly hypertonic urine can be secreted Now the thin segment of the loop of Henle appears first in birds, but is completely evolved only in mammals Indeed, Peter[55] has correlated the length of this segment in different mammals with the ability of their kidney to excrete a more or less concentrated urine

It is interesting to note that in the schematic representation of the tubules of vertebrates the proximal convoluted segment with

concerned in some way with the urea excretion, since the elimination of a urine with a much lower content of urea than the plasma is a characteristic of this sub-class Clarke and Smith[11] have recently shown that in the dogfish the filtered urea may be almost completely reabsorbed by the tubule

In view of the fact that more knowledge about the morphology and cytology of the renal tubule in many of the lower vertebrates is needed and that functional studies of many types are almost completely lacking as yet, this discussion must be limited to certain features of the comparative physiology of the kidney

The Aglomerular Kidney —The aglomerular kidney was discovered in the Lophobranchs by Huot,[34] in 1897, and described by him in 1902[33] In 1910, Audigé[2] in a general study of the kidney in teleostean fish found in the kidney of the goosefish (Lophius piscatorius) neither an arterial supply of blood nor glomeruli The aglomerular nature of the kidney in the Lophobranchs has also been confirmed by Verne[69] and Edwards[18] The kidney of the goosefish has recently been carefully studied by Marshall and Grafflin[46] and by Edwards,[18] and the common toadfish (Opsanus tau) has also been found to have an aglomerular kidney (Marshall[44]) The goosefish and the toadfish kidneys will serve as types for a description of this form of teleostean kidney

Contrary to the statements of Audigé,[2] it has been found that the kidney of the goosefish has a small arterial blood supply and a very few structures resembling renal corpuscles. Definite renal arteries, however, are absent, the main arterial supply being from minute branches of the lateral and ureteral arteries. The main blood supply is almost entirely venous, the afferent venous trunks being the caudal, caudal accessory, sub-clavian and epibranchial veins. The whole kidney can be injected from any one of the afferent veins. The large posterior cardinal vein is the only efferent vessel. Seventy-eight structures resembling glomeruli were found in one kidney, while an estimate of the number of tubules gave about 150 000 as a minimum, or about 1 pseudoglomerulus to each 2000 tubules. Grafflin[24] has shown conclusively that in the adult fish these pseudoglomeruli are non-functional, as careful study by maceration and serial section methods reveals no connection of these structures with a renal tubule. However, in the kidney of a young fish (63 mm. long), he found 94 glomeruli, all of which were connected to renal tubules. It is, indeed, interesting that these glomeruli should lose their connections with the tubules in the adult fish.

The kidney of the goosefish is composed of great numbers of irregularly convoluted tubules with definite blind endings, surrounded by a mass of pseudolymphoid tissue. The tubules may attain a length of 10 mm. or more, and have an average diameter as measured in section, of about 0.05 mm. Complete vascular injection of a kidney demonstrates freely anastomosing venous channels closely investing the outside of the tubules. The epithelium of the tubule is described by Audigé[2] as possessing a brush border throughout (with the exception of the initial collecting tubule. Edwards[18] gives drawings illustrating two segments, with and without brush border (proximal and distal convoluted tubule) but subsequently, writing of the distal convoluted tubule, he says "This convolution is present and of considerable length in the kidneys of representative animals in the chief classes of vertebrates except in that of the marine fish" (Edwards[20]). This agrees with Audigé and makes the goosefish tubule an unisegmental nephron.

The kidney of the toadfish is entirely aglomerular, no structures in the least resembling glomeruli are present. This kidney possesses a very small arterial supply, but the main afferent channels are venous. The tubules resemble those of the goosefish and are surrounded by pseudolymphoid tissue. Excluding the initial collecting tubule, it is here certain that only one type of epithelium is present, that of the proximal convoluted segment with brush border

the whole function of the kidney here is performed by a single type
of the proximal convoluted

having a large number of
glomerular structures but showing complete lack of glomerular
function by physiological tests has recently been explained by
Grafflin[24] In the kidney of the daddy sculpin (Myoxocephalus

which from careful anatomical study can be considered functional

Comparison of Function of Glomerular and Aglomerular Kidney —

certain marine teleosts but is normally much less than that from
the well glomerularized kidney of a fresh water fish Under as
nearly normal conditions as can be experimentally attained the
urine flow of the toadfish is usually below 2 5 cc per kilogram per
twenty-four hours while that of the sculpin (a glomerular marine
teleost) may be slightly higher (4 cc or less) How fundamental
such a difference is cannot be stated at the present time (Grafflin[4])
The fresh water catfish on the other hand may have a urine flow
of over 300 cc per kilogram per day

The urine of both aglomerular and glomerular marine teleosts
contains large amounts of magnesium and sulphate very small
amounts of urea and relatively large amounts of creatine and

the glomerular kidney is seen also in the case of the aglomerular
kidney Thus the urine of the toadfish may contain under some
circumstances about the same concentration of chloride as the
plasma while under normal conditions it is free of chloride with
large amounts of course still present in the plasma It would
appear then that the aglomerular tubule and indeed the single
segment with brush border can excrete a urine of the same compo
sition as that eliminated by the glomerulus and tubule together

What then are the functional differences of the glomerular and

* Grollman finds that the undetermined nitrogen of goosefish urine is mainly trimethylamine oxide and may constitute 28 to 63 per cent of the total nitrogen Hoppe Seyler[9] finds trimethylamine oxide in the urine of selachians but not in that of fresh water teleosts

aglomerular tubule? The inability of the aglomerular kidney to eliminate glucose and other sugars its specificity in the excretion of foreign substances and its ability to secrete against a higher pressure than the blood pressure are the important differences known at present A rise of blood glucose to over 500 mg per 100 cc is not followed by the appearance of glucose in the urine of the aglomerular fish while a much less degree of hyperglycemia produces glycosuria in glomerular fish (sculpin eel flounder and dogfish) Neither after the administration of phlorizin alone nor in combination with large amounts of glucose can a qualitative test for sugar be obtained in the urine of aglomerular fish A quantitative investigation of the true glucose in urine has shown that in the urine of the aglomerular fish only traces at most of glucose are ever present

It appears that none of the sugars are secreted by the aglomerular kidney Thus Jolliffe[35] and Clarke and Smith[11] have shown that xylose and sucrose although freely excreted by glomerular fish are not secreted by aglomerular fish from plasma levels of 300 to 400 mg per cent Lactose is not secreted when injected in large amounts into the toadfish

The glomerular kidney appears to excrete to some extent at least practically all diffusible foreign bodies which may be introduced into the organism such behavior is indeed demanded by the filtration theory of glomerular function This behavior in regard to foreign substances is not exhibited by the aglomerular kidney the tubule shows specificity in its behavior to these substances just as the so-called true secretory glands do A study of the excretion of phenol red and ferrocyanide as two distinct types of foreign substances has been made in representative species of the various classes of vertebrates While phenol red is readily excreted by the kidney of all vertebrates ferrocyanide fails to be secreted by aglomerular kidneys The concentration of phenol red in the urine of the toadfish may be 150 times greater than in the blood plasma but ferrocyanide when present in the plasma in large amounts can be found in the urine in only faint traces Phenol red and ferrocyanide are here taken only as types of foreign substances many others could be used Creatinine uric acid iodides nitrates thiosulphates *sulphocyanides indigo carmine and neutral red are all secreted by* the aglomerular kidney while iron salts and cyanol are not excreted Marshall and Grafflin[4] found that injected inorganic phosphate is not secreted by the aglomerular kidney but that the urine from an aglomerular fish may at times contain large amounts of inorganic phosphate This paradox is as yet unexplained Bieter[4] has also

that after an intravenous injection of a mixture of phenol red and cyanol into the goosefish the former only is excreted in the urine He had previously found that phenol red is secreted by the tubule of the frog s ki lney and that cyanol is not

Recently Bieter[4] showed that in the aglomerular kidney (toad fish) the secretion pressure taken in the ureter may be greater than the dorsal aortic blood pressure Since the main blood supply to the toadfish kidney is venous it appears that the secretion pressure can be many times as high as the blood pressure in the kidney

through the glomerulus must occur

Function of Proximal Convoluted Segment of Renal Tubule — These studies on the aglomerular kidney of fish and a comparison of its function with that of the glomerular kidney of the same order of animal prove conclusively that the tubule can secrete The absence of the excretion of glucose and other sugars the specificity in the excretion of foreign substances and the ability to secrete against pressure establish the excretion of the aglomerular kidney as being a case of *true secretion* Since the tubule of the toadfish consists of only one segment (Grafflin [24] Defrise[17]) it is obvious

of the sculpin (Fig 7 3) has shown that in this glomerular fish the proximal convoluted segment can both secrete and reabsorb (Marshall and Grafflin[46]) The sculpin kidney can be rendered functionally aglomerular by several injections of phlorizin after such injections it no longer excretes substances which are not secreted by the aglom

This would appear
convoluted segment o
merular activity is ab
glomeruli are active? The urine/plasma ratio for glucose after small doses of phlorizin used as a measure of the amount of glomer ular filtrate shows that in the marine teleost kidney a large per centage of the magnesium and sulphate of the urine as well as of injected creatinine and phenol red appear to be excreted by tubular secretion

Since the urine of a normal sculp n is free of chloride and glucose while the plasma contains these substances it follows as a corollary of glomerular filtration that these substances must be reabsorbed by the proximal segment Reabsorption of water by the proximal segment is prove l by the fact that the urine/plasma ratios for glu

cose and xylose can reach values over 2 (neither of these substances is secreted by the tubule of the sculpin) * By direct methods White and Schmitt[71] had previously localized the reabsorption of chloride and glucose by the proximal segment of Necturus

Primitive Function of the Glomerulus and Adaptation of Glomerular Development in Animals to Habitat —Sixteen species of fish belonging to six families are now known to have aglomerular kidneys (Marshall[44]) These all belong to the group of marine teleosts Why do these fish have aglomerular kidneys? This question may possibly be answered by some important work of Homer W Smith Smith[67] finds that in teleosts about 6 to 10 times as much nitrogen is excreted by the gills as by the kidneys Moreover, he[6] has found that marine teleosts swallow sea water, absorb from the intestine a large amount of the water and salts and excrete by means of the gills a much greater percentage of this water and certain salts than is eliminated by the kidneys † Fresh-water teleosts, on the other hand absorb water from their environment probably by way of the gills and excrete large quantities by way of the kidney On the basis of this work Smith has suggested that the aglomerular state of certain marine teleosts is due to their peculiar water cycle resulting in the excretion of only small amounts of water by way of the kidney ‡ If this view is correct, glomerular development should be related to the need for water excretion by the vertebrates generally and a preliminary survey of the vertebrate kidney has been made from this standpoint (Marshall and Smith[47])

The general theory which has been developed may be briefly outlined as follows The excretory organ or kidney of the protovertebrate ancestor of the fish was presumably aglomerular,§ and in the course of the evolut [illegible]
was developed in response [illegible]
taken up in large amounts [illegible]
these animals lived With a migration to the sea, the need for the glomerulus ceased because water was no longer being taken into the organism in large amount and because the gills could excrete considerable water, due to the difference in the external medium to which they were now subjected Hence the kidney of the marine

* Marshall and Grafflin[48] concluded that the same histological type of cell could both [illegible]
clude [illegible]
of G [illegible]

† [illegible]
and water by the perfused gills of the eel in sea water Keys and Willmer[44] [illegible]

‡ [illegible] toadfish never develops glomeruli is interesting in this connection

§ Nussbaum[61] and Armstrong[1] present definite evidence for secretion in the aglomerular pronephric tubule of fish embryos

has no need for glomeruli unless a new purpose is served by them The same holds true for the birds and mammals

If we examine the character of the glomerular development in the different groups of vertebrates, we find that it agrees fairly well with the above hypothesis
ment of glomerular surface
noans, amphibians and mam
teleosts, reptiles and birds it is distinctly poor If we adopt a subsidiary hypothesis that in the mammals (and to some extent in the lower vertebrates) the primitive water-excreting function of the glomerulus has been secondarily diverted to the excretion of waste products, we see that the known facts agree well with the hypothesis

Relation of Comparative Data to Theories of Urine Secretion — Let us now see what bearing these fragmentary observations on the comparative physiology of the kidney have upon current theories of urinary secretion The ability of the glomerular kidney to eliminate to some extent practically all soluble and diffusible substances which may enter the blood stream, and the necessity of the glomerulus for such a process argues for the filtration theory of glomerular function The abundant other evidence for filtration warrants the acceptance of this theory, with the reservation that possibly the glomerulus may at certain stages of development secrete as well The high cubical epithelial cells of the visceral layer of Bowman's capsule seen at one stage in the embryonic kidney, the cubical epithelium in certain renal corpuscles of the opossum's kidney described by MacNider,[43] similar findings in the kidney of the mouse (Standfuss[64]) and the frequency with which rather high epithelium on the visceral layer of the capsule occurs

indeed, in the proximal segment That this same proximal convoluted segment with brush border can also transfer substances from the blood and lymph to the lumen of the tubule is proven by a consideration of the morphological and functional studies on the toadfish kidney which have been outlined The occurrence of this proximal convoluted segment with brush border in the kidney

* Osawa[54] states that in the kidney of Sphenodon the visceral layer of Bowman s capsule is composed of high cubical cells

Certain calculations in regard to glomerular filtration in the fowl's kidney may be of interest The total numbers of glomeruli in the [illegible] were found to [illegible] the renal cor- [illegible] ures with data for a rabbit of about the same size A 2400-gm rabbit was found to have 414,000 glomeruli in both kidneys, the average diameter of the renal corpuscles was 142 μ Thus, the glomeruli in the fowl are about twice as numerous as in the rabbit and of about one-half the size Hence, allowing for the much less developed vascular tuft in the fowl, it is certain that the total glomerular surface of the chicken is considerably less than that of a rabbit of the same weight But, on the theory that glomerular filtration furnishes all of the constituents of the fowl s urine, difficulties are encountered A calculation from the urea ratio of Addis (Taylor, Drury and Addis[63]) shows that about 250 cc of glomerular filtrate per hour is required in a 2500-gm rabbit to account for the urea eliminated in the urine, about 300 to 350 cc of filtrate would be required to account for the excretion of creatinine (MacKay[4]) In the case of fowl the figures on uric acid in the plasma and urine require from 1400 to 3300 cc of glomerular filtrate per hour to explain the uric acid elimination on the filtration-reabsorption hypothesis alone In other words about ten times as much filtration is demanded from the filtering surface in the bird, which is much less extensive than that in the rabbit It is doubtful if differences in blood-pressure or colloid osmotic pressure could increase the filtration to this extent, especially as the visceral epithelium of Bowman's capsule in the chicken appears to be much thicker than the same structure in the rabbit

The situation in the arid reptiles, such as snakes and lizards, is apparently very similar to that in the birds, but practically no functional studies have been made of the reptilian kidney † Here, the small renal corpuscles are poorly vascularized, and hence the total glomerular surface must be small A comparison may be made of the relative extent of glomerular surface in the horned toad (Phrynosoma cornutum) and the common frog (Rana pipiens) Hayman[76] has reported glomerular counts on the kidney of the frog of 1592 to 5260 per kidney, the number most frequently being around 2000 Since the size and weight of the frogs is not given,

* [illegible]

in both kidneys

† Bordley and Richards[7] report that the analysis of glomerular fluid taken from the renal corpuscles of snakes shows the uric acid concentration to be of the same order as in the blood plasma

we cannot tell to what extent this factor accounts for the variable counts We find a 19 5-gm frog to have 1608 glomeruli, a 26 5-gm frog, 2220, a 295-gm bullfrog, 6400, and a 268-gm animal, 8150 We conclude that large frogs have in general a greater number of glomeruli than small ones, and that for frogs of 20 to 25 gm the number of glomeruli per kidney is about 2000 Four horned toads, varying in weight from 16 9 to 24 gm had 1575 to 2425 glomeruli per kidney It is thus obvious that the kidney of the horned toad does not contain more glomeruli than that of a frog of the same [illegible] 20 gm [illegible] of the [illegible] a poor capillary development, it is clear that the glomerular surface in the latter animal is much less than in the former The total capillary surface of a glomerulus can be taken to vary as its volume if it is entirely filled with capillaries of the same diameter But the frog's glomerulus is more vascular than that of the horned toad so this assumption gives too high a value for the capillary surface of the latter Even on this basis, we find that the total glomerular surface of the horned toad is only about 7 per cent that of a frog of the same size

An arid-living lizard (Iguana iguana Shaw) has recently been investigated The number of glomeruli in the kidney appears to [illegible] here much reduced A comparison of the amount of glomerular filtrate, as measured by the glucose ratio after phlorizin with the amount of uric acid excreted indicates that in the reptiles as in the birds, the major portion of the uric acid is excreted by tubular secretion (Marshall[46])

In the mammals we find excellent glomerular development This, together with the complete development of the loop of Henle, suggests that the primitive water-excreting function of the glomerulus has been almost completely modified and the glomerulus now serves as the main route for the excretion of the normal constituents of the urine * This agrees with the idea that, in mammals filtration and reabsorption play a major part in the excretion of urine, and that secretion exists only as a relic of a primitive process (Mayrs,[43] Marshall[44]) To explain the formation of hippuric acid and ammonia by the mammalian kidney would seem to necessitate secretion by the tubule, and certain other substances also appear to be secreted

* Smith[52] has pointed out that the filtration reabsorption mechanism in the mammal does not owe its existence to any superiority of this method over tubular secretion but is a consequence of the evolutionary history of the vertebrates

From the work of Jolliffe, Shannon and Smith[37] on the use of non metabolized sugars to measure the glomerular filtrate in mammals it is probable that the filtration-reabsorption mechanism is sufficient to excrete practically all of the normal constituents of the urine On the other hand, there is now proof that a very large percentage of certain substances is excreted by tubular secretion in the mammal It is certain that a large amount of phenol red is excreted by tubular secretion in the dog (Marshall[44]) * Using xylose as a measure of the glomerular filtrate, Shannon, Jolliffe and Smith[61] have shown that nearly 50 per cent of ingested creatinine may be excreted by tubular secretion in the dog, and Jolliffe and Chasis[36] find that in the human subject about 42 per cent of ingested creatinine is secreted

Since the evidence is becoming very strong indeed that glucose after phlorizin or xylose can be used to measure the glomerular filtrate in different classes of vertebrates (Jolliffe, Shannon and Smith [37] Clarke and Smith [11] Marshall[44]) † we can give a preliminary table of magnitude of the glomerular filtrate in different animals

all certain that weight or surface area is the proper basis on which to compare different classes of animals The conditions under which the data for calculation of the filtrate have been obtained are not comparable for all the animals and, since Shannon, Jolliffe and Smith[61] have shown that diet can alter the glomerular filtrate in the dog more than 300 per cent it is obvious that quantitative comparison of the present figures is not justified Nevertheless, Table 3 does emphasize some of the points which have been dis-

* Doctor Shannon informs me that by the use of xylose to measure the glomerular filtrate in the dog he has found that a large percentage of the total phenol red excreted from low plasma concentrations cannot be accounted for by glomerular filtration alone Chambers and Kempton[10] have developed an ingenious method of studying renal function by the use of tissue cultures and a micro manipu

an agreement as was reported by Jolliffe Shannon and Smith[37] Prof Homer W Smith on the other hand informs me that he and his co workers have accumulated considerable additional evidence of the validity of the use of xylose or sucrose to measure the glomerular filtrate both in the dog and in the human subject Pitts has recently found that when the plasma level of inorganic phosphate is raised by injection the concentration ratios of inorganic phosphate and xylose approach one

TABLE 3 —URINE FLOW WATER REABSORPTION AND GLOMERULAR FILTRATE

	Ur ne flow	U/P ratio glucose or xyl se	Glomerular filtrate	Remarks
	cc per k lo per hour		*cc per k lo per hour*	
Elasmobranch Squalus acanthias (dogfish)	0 18– 1 6.	2 15– 6 71	1 21– 4 06	From Clarke and Smith [1] Xylose
Teleost Myoxocephalus octodecimspinosus (sculpin marine)	0 11 0 98	0 51– 2 75	0 13– 0 96	From Marshall and Graffin [46] Glucose after phlorizin
Ameiurus nebulosus (catfish fresh water)	6 4 13 6	1 25– 1 90	10 0 17 3	From unpub lished observations Xylose
Amphibian Rana cat esbiana	1 5 –20 7	1 16– 3 00	2 8 –40 0	From Marshall [46] Xylose
Reptile Inguana iguana	0 20– 1 23	1 5 – 4 9	0 3 – 3 8	From Marshall [46] Urethane glu cose after phlo rizin
Alligator mississippi ensis	0 43– 1 0	2 6 4 2	1 5 – 3 4	From Burgess Harvey and Marshall [9] Water diuresis xylose
Bird Chicken	2 8 – 7 5	4 7 –17 3	23 5 91 6	From Marshall [46] Urethane glu cose after phlo rizin
Chicken	2 0 –17 7	5 2 – 18 0	36 6 –93 0	From Burgess Harvey and Marshall [9] Water diuresis and pituitary ex tract Xylose
Mammal Dog	2 7 –19 3	7 3 –63 2	9. –327	From Jolliffe Shannon and Smith [2] Water diuresis xylose and raffi nose

cussed above The very low values for the urine flow and glomer ular filtrate of the marine teleosts and reptiles stand in contrast to the high flow and high filtration rate in the amphibians and fresh water teleosts [illegible]
for all animals below
poor water-reabsorptic
ratios, beginning in the bird and reaching its maximum in certain

mammals shows the importance of the loop of Henle for efficient tubular reabsorption of water. *Of course in non-diuretic dogs the glucose or xylose ratio can reach very much higher values than those given in the table.*

Blood Supply of Kidney.—A consideration of the blood supply to the kidney of different classes of vertebrates appears to confirm the ideas expressed above. *In the aglomerular kidney of the marine*

of the Cyclostomes) below the mammals * there exists a double blood supply to the tubule: an efferent glomerular vessel and a renal portal system (Jourdain[38] Noll[50] Spanner[63]) this is quite to *be expected if tubular secretion plays a greater role in the lower vertebrates than in the mammals.* It is generally believed that the bloods of the efferent glomerular vessel and of the renal portal system mix freely and supply all parts of the tubule but the functional investigations of Scheminzky[60] and Oliver and Shevky[53] seem to show that this idea of the blood supply of the tubule of the frog's kidney may have to be modified. Their findings indicate that the distal convoluted segment is supplied by *the efferent glomerular* vessels and the proximal convoluted segment by branches of the renal portal vein. Policard[56] states on anatomical grounds that this is the case. A more complete and careful investigation of this point should be made.

Histological Evidences of Secretion. *Many observers have de*scribed what they believe to be histological evidences of secretion in the renal cells of the lower vertebrates. Thus rather definite granules or globules of material are described as in the process of extrusion from the cells of the tubule and mesonephric duct of Myxine (Conel[12]) *and recently Herring[27] has reported what he* regards as histological evidence of secretion in the kidney of the skate. Defrise[17] and Oliver and Lund[52] are the most recent writers to present cytological changes in the renal epithelial cells of the lower vertebrates which they believe to be indicative of secretion. The histological evidence for *secretion in the cells of the sexual* segment of the kidney of male snakes and lizards (Regaud and Policard[58] Cordier[13]) and in the renal cells of nest building fish like the stickleback (Hess[28]) would seem to be quite definite.

In conclusion it may be stated that this *fragmentary account* of certain phases of the comparative physiology of the vertebrate kidney appears to indicate the value of pursuing this line of inquiry to obtain an understanding of renal function from a broad biological

* Das[4] states that the bird has no true renal portal system similar to that of fishes amphibians and reptiles

viewpoint and to evaluate properly much of the work on the lower animals in its relation to renal function in man From what has been presented we conclude that glomerular filtration tubular reabsorption and tubular secretion all probably occur to some extent in all vertebrate kidneys (except the aglomerular kidney) The relative importance of the filtration reabsorption mechanism and of tubular secretion of any given substance depends on the substance in question the particular species of animal under con [illegible] vation [illegible] under [illegible] normal urinary constituents it is possible that under certain pathological conditions the more primitive secretory process in the tubule may be of major importance *

References

1 Armstrong P B 1932 The embryonic origin of function in the pronephros through differentiation and parenchyma vascular association Am J Anat 51 157 1933 Development of an aglomerular pronephros Anat. Rec 55 45 (Suppl)

2 Audigé J 1910 Contribution à l étude des reins des poissons téléostéens Arch zool expér et gén 4 275

3 [illegible]

[illegible]

7 [illegible]

[illegible]

9 Burgess W W Harvey A M and Marshall, E K Jr 1933 The s te of the ant d uretic action of pitu tary extract J Pharm and Exp Therap 49 237

10 Chambers R and Kempton R T 1933 Indicat ons of function of the ch ck mesonephros in tissue culture with phenol red J Cell and Comp Physiol 3 131

11 Clarke R W and Smith H W 1932 Absorption and excretion of water and salts by the elasmobranch fishes III The use of xylose as a measure of the glomerular filtrate in Squalus acanthias J Cell and Comp Physiol 1 131

12 Conel, J I 1917 The urogenital system of myxino ds J Morphol 29 75

* This same idea is impl ed by MacN der[43] who states that future studies of the details of the circulat on in the patholog al kidney may alter the conception that an obliterat on of glomerular vessels results in atrophy of the tubule Dr MacN der informs me by a personal communication that he has very definite reasons to believe that under certain pathological cond t ons a blood supply is furnished the tubular tissue of the kidney ndependent of the glomeruli

13 Cordier, R 1928 Études histophysiologiques sur le tube urinaire des reptiles, Arch de biol, 38, 111
14 Crane, M M 1927 Observations on the function of the frog s kidney, Am J Physiol, 81, 232
15 Cushny, A R 1926 The Secretion of the Urine, London, Longmans, Green & Co
16 Das, B K 1931 Observations on the "renal portal" perfusion in etherized birds, J Morphol, 51, 309
17 Defrise, A 1932 *Cytophysiological studies on the nephrocytes of*

sse und
3
mikr -

Am J
Physiol, 66, 8

24 Grafflin, A L 1929 The pseudoglomeruli of the kidney of Lophius piscatorius, Am J Anat, 44, 441 1931 The structure of the renal tubule

Anat Rec, 15, 305
32 Hufner, C G 1866 Zur vergleichenden Anatomie und Physiologie der Harncanälchen, Inaug Diss, Leipzig
33 Huot, A 1902 Recherches sur les poissons lophobranches, Ann sci nat zool, 14, 197
34 Huot, E 1897 Sur les capsules surrenales, les reins le tissue lymphoide ... Compt rend Acad d sc 124 1462
and aglomer-
secretion of
he excretion
measurement

38 JOURDAIN S 1859 Recherches sur la veine porte rénale Ann sci nat zool 12 134
39 KEYS A B 1931 Chloride and water secretion and absorption by

440 1929 The aglomerular kidney of the toadfish (Opsanus tau) Bull Johns Hopkins Hosp 45 95 1930 A comparison of the function of the
1931 The secre
sol 99 77 1932
29 971 The secre
ne secretory function

phosphate by the aglomerular kidn
47 MARSHALL, E K JR AND

50 NOLL A 1924 Die Excretion Wintersteins Handb d vergl Physiol 2 760
51 NUSSBAUM M 1886 Ueber den Bau und die Thatigkeit der Drusen V Zur Kenntnis der Nierenorgane Arch f mikr Anat 27 442
52 OLIVER J R AND LUND E M 1933 Cellular mechanisms of renal secretion I The structural phase of the secretory mechanism J Exp Med 57 435
53 OLIVER J R AND SHEVKY, E 1929 A comparison of manner of excretion of neutral red and phenol red by frogs kidney J Exp Med 50 15 1930 The relation of particle size to mechanism of dye excretion by the kidney Am J Physiol 93 363
54 OSAWA G 1897 Beitrage zur Lehre von der Eingeweiden der Hatteria punctata Arch f mikr Anat 49 113
55 PETER K 1909 Untersuchungen über Bau und Entwickelung der Niere Jena Gustav Fischer
56 POLICARD A 1910 Le fonctionnement du rein de la grenouille Arch d anat micr 12 177
57 POLICARD A AND MAWAS J 1906 Le canalicule urinaire des téléostéens Bibl anat 15 215

60 SCHEMINZKY F 1929 Ueber die Harnbildung in der Froschniere XVII Mitteilung Die Farbstoffsekretion der 2 Abschnitte Pflugers Arch 221 641

61 SHANNON, J A, JOLLIFFE, N, AND SMITH, H W 1932 The excretion
diets, feeding, etc, upon
101, 625, The excretion of
of exogenous creatinine,

62 SMITH, H W 1
of fish, J Biol Chem,
and salts by marine tel
of the composition of
evolution of the verteb
and its evolution in the issues, Quart Rev Biol, 7, 1

63 SPANNER, R 1924 Bau und Kreislauf der Reptiliennere, Ztschr f Anat, 76, 64

64 STANDFUSS, R 1908 Vergleichend histologische Studien an den Malpighischen Korperchen der Niere der Wirbeltiere, Arch f mikr Anat, 71, 116

65 STARLING, E H, AND VERNEY, E B 1925 The secretion of urine as studied on the isolated kidney, Proc Roy Soc, B, 97, 321

66 SUZUKI, T 1912 Zur Morphologie der Nierensekretion, Jena, Gustav Fischer

67 TAMURA, K, MIYAMURA, K, NISHINA, T, NAGASAWA, H, FURKUDA, F, AND KISHI K 1927 The seats of excretion of dyes in the kidney, Jap J Med Sci Trans, 1, 275

68 TAYLOR, F B, DRURY, D R, AND ADDIS, T 1923 The relation between the rate of urea excretion and the size of the kidneys, Am J Physiol, 65, 55

69 VERNE, J 1921–1922 Contribution à l étude des reins aglomérulaires
, 18, 357
ive study of the

absorption in the

CHAPTER IV

THE FILTRATION REABSORPTION THEORY OF KIDNEY FUNCTION AND ITS USE IN THE CLINIC

By POUL BRANDT REHBERG PH D

Introduction —Since *Cushny* wrote his monograph on the secretion of the urine the filtration reabsorption theory has been the point around which the discussion of this question has largely centered Most of the adherents of the old secretion theory have more or less adopted parts of this later theory and fitted it into the older one Very few now hold that the excretion of urine is a process of purely secretory character that is that both glomeruli and tubules secrete It is a widely accepted view that the process going on in the glomeruli is an ultrafiltration and it is also widely accepted that substances are reabsorbed again from the filtrate by the tubules The adherents of the filtration theory on the other hand must also admit that *secretion does take place in the kidney* When a substance is excreted in the urine in an amount many times exceeding that which can have been carried to the kidney by the blood flow during the same period the assumption of secretion seems unavoidable

Definition of Terms —Before proceeding it is best to define what we mean when we use the terms filtration reabsorption and secretion in connection with processes in the organism generally

As *filtration* we term a transport of fluid across a membrane through the action of hydrostatic pressure alone If the fluid is separated from colloids by the filtration we speak of *ultrafiltration*

Reabsorption is usually defined as a process by which a substance water or solid is transported back into the blood again after having in some way left it As this transport back may be effected in different ways we may speak of active and passive reabsorption

Active reabsorption occurs if the cells through which the transport takes place use energy to help the passage The transport may then take place against the concentration gradient or may proceed faster than ordinary diffusion would allow

Passive reabsorption takes place when a substance is brought back into the blood without the use of energy by means of pressure and concentration differences existing between the fluid and the blood Water may in this way be sucked into the blood if the colloid osmotic pressure of the latter is high enough to overcome the blood pressure

If solid substances permeate through cells into the blood because their concentration is higher outside this is a *simple process of* diffusi

By

natur

the outside through gland cells The main point in this case is also whether the transport takes place at the expense of energy furnished by the vital activity of the cells According to this definition secretion occurs (1) if a substance is *transported from* blood to the outside against a pressure or concentration gradient (2) if the substance transported is synthesized by the cells from constituents of the blood and (3) if a substance is stored in concentrated form in the cells and later excreted

What has been proved? Which of these processes have been shown to exist in the kidney? Direct study of fluid within the excreting units of the kidney glomerular capsules and tubules—are extremely difficult and until now have been made only in lower animals Practically all that we know we owe to the work of Richards and his school Through their work it has been made highly probable that the fluid excreted in the glomerular capsule is an ultrafiltrate of the blood It is protein free its total molecular concentration is the same as that of blood the total amount of electrolytes is the same It contains urea sugar chlorine potassium and injected dyes Experiments by White show that the formation of the fluid is highly dependent on the equilibrium between colloid osmotic pressure plus capsule pressure on one hand and glomerular capillary pressure on the other hand When these forces are in equilibrium fluid excretion practically stops and the experiments of this author to the writer s mind proves that ultrafiltration is the normal function of the glomeruli

Wearn and Richards showed that even when the urine of the frogs contained no sugar or chloride these substances were present in the glomerular fluid Reabsorption of these substances has *thus been proved and also the reabsorption of water Secretion* too has been demonstrated The synthesis of hippuric acid by the kidney is secretion and the far more important formation of ammonia must also be called secretion But secretion in the sense of transport of preformed substances from the blood through the tubule cells into the urine with the use of cell energy has not been proved Nor has a storing of substances with subsequent excretion

ption and secre-
nce between the
r their explana-
hold that vital
activity is necessary *i e* that energy is used But while the

secretion theory holds that practically all the energy is used in transporting substances from the blood through the tubule cells out into the urine—that is for secretion—the other theory holds that the main use of energy is for transport in the opposite direction—that is for reabsorption And while the secretion theory assumes that the amount of fluid excreted in the glomerular capsules is of about the same quantity as that of the urine during the same period the filtration theory assumes that far larger quantities are filtered so large in fact, that all the solids of the urine are present in the filtrate and most of them in far greater quantities than in the ultimately formed urine

MAGNITUDE OF THE FILTRATION

How large is the necessary quantity of filtrate? The quantity is certainly larger than usually assumed In a number of experiments the author[17] tried to raise the creatinine content of the blood to such a level that it could be estimated fairly accurately At the same time the creatinine excretion was followed with the result that creatinine was found to be excreted in amounts so large it was necessary to assume a filtration of 120 to 180 cc per minute or even more The result has later been confirmed (Holten and Rehberg Tolling Poulsson) Creatinine is at the same time concentrated more than any other substance a concentration ratio of 400 has been encountered

But is it possible to filter 180 cc per minute through the glomeruli that is more than 250 liters in a day or about 100 times the total amount of blood plasma? The filtration or rather ultrafiltration through a membrane depends on different factors the surface area and character of the membrane and the filtration pressure How large is the surface of the glomeruli? To get an answer to this question we must know the surface of a single glomerulus and the total number of glomeruli in the human kidney Both questions have been answered by the work of Vimtrup

Vimtrup has shown that the glomeruli are even better adapted for filtration than is usually assumed Each glomerulus consists of a number of capillary loops about 50 in all every capillary loop being covered with epithelium The pictures usually given of the

for one glomerulus

Vimtrup has also given more reliable figures for the number of

glomeruli than the older data His method has been controlled by three total counts of glomeruli in a kidney of rat, cat and man The result is that the number of glomeruli in the human kidney may be put at 1,000,000 The total surface available for filtration would then be 1 5 sq m Over this surface the blood is separated from the capsule by a membrane the thickness of which does not perhaps exceed 1 μ

Now the experiments of Landis have shown that the filtration through mesenterial capillaries in the frog can rise to 9 1 cc per 100 sq cm for a pressure of 1 atmosphere before the capillaries become permeable to protein Assuming the blood-pressure in [illegible] er, we should get [illegible] As the permea- [illegible] one must admit that the formation of a filtrate in amounts of even 150 cc per min is possible

We must, therefore, if we want to keep up the filtration-reabsorption theory, postulate that the first step in the excretion of the urine is the formation of 150 cc of ultrafiltrate each minute From this filtrate most of the water is reabsorbed along with different substances According to the formulation of the theory given by [illegible]

tained Experiments by Mayrs showed that part of the filtered urea was reabsorbed and was reabsorbed in varying concentrations Experiments by the author confirmed this and showed that for chlorine, also, the concentration must vary within wide limits in the reabsorbed fluid Recent experiments by Ni and the author have shown that sugar behaves in the same way The reabsorbed fluid is not of constant composition, but varies according to the composition of the filtrate

THRESHOLD SUBSTANCES

The substances present in the reabsorbed fluid Cushny called "threshold bodies" The use of this term should indicate that when their concentration in the *blood* is *below* a certain *threshold* value they are not present in the urine Following the experiments of Mayrs, which showed that urea is reabsorbed, he, and later Cushny, concluded that urea is a threshold substance Now the experiments of the author showed that creatinine is concentrated more than all other substances, except perhaps *a few which become* concentrated to the same degree This means that all other substances must become reabsorbed to some extent, *i e*, that they are threshold substances But if this is so, the original simple

heory of Cushny has lost most of its attractiveness and necessarily becomes very complicated The mechanism of the reabsorption which Cushny conceived of corresponding to our term active reabsorption becomes very difficult to understand when it includes nearly all substances The author therefore, tried to modify the theory so as to fit these new facts, attempting to retain the simplicity of Cushny s original theory This led to the distinction between active and passive reabsorption which latter term here means backdiffusion The reasons for this distinction may perhaps be made clear in the following way Suppose we send a fluid con

be a substance for which the walls are extremely permeable this substance will not be concentrated at all As soon as any concentration difference between the fluid within the tube and that outside arises diffusion will take place and eliminate the difference The substance will leave the end of the tube in the same concentration as it entered but the total amount will be much reduced—to the same extent as the water has been reduced

TABLE 4

(Showing the concentrations of A alcohol (a highly diffus ble substance) B urea (a moderately diffus ble substance) C creatinine (a non diffusible substance) and D a threshold substance (one actively reabsorbed) after passing along a semipermeable tube through the wall of which water is being absorbed)

		A Al ohol)		B (Lrea)		C (Creat n ne)		D (Threshold sut st)	
		Mg	Mg c_o	Mg	Mg	Mg	Mg	Mg	Mg c_o
Filtered	100 cc	10 0	10	10	10	10	10	10 0	10
Reabsorbed Remaining	50 cc 50 cc	5 0	10	9	18	10	20	4 0	8
Reabsorbed Rema n ng	90 cc 10 cc	1 0	10	8	80	10	100	0 5	5
Reabsorbed Remaining	99 cc 1 cc	0 1	10	5	500	10	1000	0 03	3

Let C be a substance toward which the walls of the tube are impermeable When water is absorbed this substance will become concentrated and will leave the end of the tube in a concentration which is an index of the degree to which water has been reabsorbed Suppose, finally that B is a substance toward which the walls are moderately permeable B will then be concentrated, but part of it will diffuse back and when it leaves the end of the tube it will be concentrated perhaps only one-half as much as C which means that only one-half of the substance is retained in the fluid while the other one-half has diffused back The more concentrated the fluid becomes in regard to C, that is, the more water is reabsorbed,

the more will B become concentrated but more of B will also diffuse back so that the proportion is diminished

If the active process taking place in the tubules of the kidney is reabsorption of water while the walls of the tubules vary in degree of permeability toward different substances we can explain the behavior of substances which like A are not concentrated at all Such substances are alcohol and acetone If the walls of the tubules are impermeable to one or more substances these will behave like C to be concentrated more than others and their final concentrations will be an index of the degree of concentration of the urine Substances of this kind are found in creatinine and sulphates In between these extremes we find compounds toward which the walls of the tubules are permeable to some degree and which are therefore somewhat concentrated though never as much as creatinine but the more concentrated creatinine is the more concentrated will these substances be Urea is such a compound

presen

or be

necessary to assume an active reabsorption Substances for which this is necessary we call threshold substances but their number is not great

THE MODIFIED THEORY

The modification of the filtration reabsorption theory made necessary by the facts already mentioned may be formulated thus The

5 Secretion of substances not preformed in the blood

EXPERIMENTAL EVIDENCE

With this scheme as a working hypothesis a number of experiments have been performed partly by the author and co workers partly by others The results of these studies which have so far confirmed the theory shall be briefly discussed

1 **Creatinine as Index of the Filtration Rate** The basis of all the experiments is the assumption that creatinine can be used as an index of the filtration rate The calculation of the filtration

rate per minute is carried out by means of the following formula, F = CV, where C is the concentration ratio of creatinine—i e, $\left(\frac{\text{percentage in urine}}{\text{percentage in blood}}\right)$—and where V is the urine volume per minute

If creatinine is really filtered through the glomeruli and does not diffuse back through the tubules, it should be possible to demonstrate certain facts which must follow from this (*a*) If a substance is excreted through the glomeruli by an ultrafiltration process the excretion of the substance shall be dependent on the filtration pressure As the filtration pressure depends on the colloid osmotic pressure of the blood which counteracts it, the excretion of creatinine should vary inversely with the colloid osmotic pressure of the blood Such is the case In experiments together with Ni, the author has shown that in changing posture, the colloid osmotic

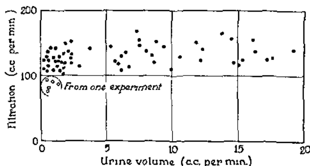


FIG 8—Independence of filtration and diuresis From experiments on 1 normal subject (Holten and Rehberg Acta med Scand)

pressure of the blood varies much and the excretion of creatinine

altered at the same time, but the change in the colloid osmotic pressure is by far the dominating one (*b*) The excretion of a substance which does not diffuse back shall be independent of the degree of concentration of the urine As volume of urine and degree of concentration of urine vary in opposite directions, it means that the excretion shall be independent of the volume of the urine Creatinine practically is so (*c*) If other substances could be demonstrated to follow creatinine in concentration ratio, this would mean that they, too, do not diffuse back

Poulsson, in a valuable contribution, demonstrated that the concentration of inorganic sulphate in the urine is proportional

to the creatinine concentration index Poulsson has moreover contributed one of the strongest arguments brought forward in support of the theory namely, that in the completely phloridzinized dog sugar is concentrated very nearly to the same degree as creatinine The only explanation possible under the secretion theory namely that a phloridzinized kidney begins to secrete sugar at *nearly the same rate as that at which it secretes creatinine and* sulphate is of course possible but certainly not probable *

2 **Threshold Bodies** —The excretion of two threshold bodies has so far been studied

(*a*) As mentioned above Poulsson demonstrated that sugar in the urine in the phloridzinized dog is not reabsorbed and experiments by Mi and the author threw light on the glucosuria caused by a high sugar level in the normal dog Our experiments showed that sugar is reabsorbed even when the concentration of sugar is high above the normal and even reabsorbed in increased amounts but that the increase in reabsorption does not parallel the increase in filtration consequently more and more is excreted

The reabsorption seems to be limited because the tubule cells are able to reabsorb sugar only against a certain concentration difference of sugar When this limit is reached no more is reabsorbed and the remaining sugar is concentrated with the urine and excreted Sugar is not reabsorbed in constant concentration but the percentage in the reabsorbed fluid increases with increasing blood sugar

(*b*) *Chloride* —The reabsorption of chloride has been shown to be regulated in such a way that the kidney tries to keep up a chloride level of 370 mg per 100 cc[18] At this level chloride is excreted [illegible] concentration and the

only traces of chloride are left in the urine If the chloride in the blood is increased the percentage in the reabsorbed fluid is increased also but not so much and more and more chloride is excreted Under these circumstances it is hard to distinguish between active and passive reabsorption and it is not possible to say how much can be explained by mere backdiffusion but probably all active reabsorption is stopped when the chloride level reaches 400 mg per cent

* Hober has demonstrated that creatinine is filtered through the glomeruli in the frog and that no creatinine is secreted by the tubules

reasoning If a substance is concentrated only 100 times when the urine has been concentrated 150 times it means that one-third of the filtered amount has diffused back, while two thirds are excreted With a concentration index of 150 the urinary volume will be approximately 1 cc per minute If the concentration is only one-

obtained in this way closely resembles that obtained experimentally for the excretion of urea The experimental curve differs from the theoretical only in a somewhat larger backdiffusion with high urinary volume The deviation is probably to be explained by an increase in the surface through which the diffusion takes place—an increase caused by the dilatation of the tubules when the diuresis is large

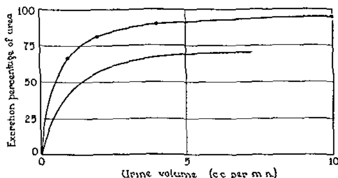


Fig 9 —Curves showing the relation between urea excretion and urine volume Upper curve drawn on the assumption that the back diffusion at a urinary volume of 4 cc is 10 per cent Lower curve the values actually found (Holten and Rehberg Acta med Scand

The most significant fact is that when the volume of urine is less than 2 cc the excretion of urea shall be highly dependent on the urinary volume and increase with it while it shall be almost independent at greater diuresis This is exactly what Van Slyke and co-workers have demonstrated and the fact that the working hypothesis put forth here gives a natural explanation of this excretion curve shows its usefulness

4 **Secretion** —Folling has used the creatinine method to confirm the finding of Nash and Benedict that ammonia excretion cannot be accounted for by filtration but that true secretion—that is synthesis—must take place in the kidney

5 **Other Experiments** —Other experiments not having a special bearing on the theory might perhaps be mentioned

Poulsson[15] has beside the experiments on phloridzin glucosuria already mentioned made a study of the influence of pituitrin on the function of the kidney He concluded that glomerular filtration rate is not markedly changed so the decrease in diuresis must be brought about by an increase in reabsorption Moreover he demonstrated that urea under the influence of pituitrin diffuses back to a larger extent than usual a fact which he explains by assuming that the increased water reabsorption takes place in the upper part of the tubules so that the concentrated urea has to pass *through a longer part of the tubules*

Experiments in the laboratory of Orbeli in Leningrad show the blood flow through the kidney of dogs is always large enough to allow the formation of the amount of filtrate necessary to explain the excretion of creatinine (Personal communication)

As a summary of this part we may say that the physiological experiments made heretofore are in such good agreement with the theory that it seemed justifiable to test it in the clinic partly in elaborating functional tests partly in explaining the pathological changes of function met with Since the understanding of the function of the diseased organ is impossible so long as we do not *attempt to look at it as modified normal function and since every* physiological theory of the function of an organ must be able to offer some explanation of its dysfunction as well we might hope through a clinical study to gain results of value to the theory itself

THE PATHOLOGICAL FUNCTION OF THE KIDNEY *

When we want to explain the pathological function of the kidney by means of ... *filtration* + re-
absorption o... ision + secre-
tion of u... the different
processes inv... ut when they
have failed ...

by coalescence of the individual capillary loops (b) Filtra... be reduced if the character of the membrane is changed *i e* if it is thickened (c) If the filtration pressure is reduced either because *the blood pressure itself is low* or because the colloid osmotic pressure of the blood is too high the filtration will be decreased ... the total

ing to the extent to which they diffuse back The excretion of substances not diffusing back, like creatinine and sulphate, will be reduced in proportion as the filtrate is reduced Substances which *diffuse back are reduced in amount in the filtrate, but their excretion* may easily be normal if a more dilute urine is excreted In this way decreased water reabsorption can have a compensatory action on the excretion of the diffusible substances, while the non-diffusible, like creatinine, are not influenced Their concentration in the blood [illegible]

The filtration pressure may be reduced either for the reasons mentioned or because the intracapsular pressure is raised The intracapsular pressure depends on the force necessary to drive the filtrate and later the urine through the tubules How large the necessary pressure is we do not know—we do not even know for sure if the tubules have cilia which take part in the transport of the fluid * But if the reabsorption of water is decreased the amount of fluid which has to be driven out is larger and the intracapsular pressure will rise so that filtration is decreased This means that pathological changes in the tubules which affect their *reabsorption ability will influence the filtration through the glomeruli* Normal reabsorption is a condition for normal filtration

Testing of Glomerular Function —When we want to test the function of the glomeruli we can according to what has been said, do so by determining the amount of blood cleared of creatinine per minute Our procedure has been the following

[illegible]

blood sample drawn

The volume of this last sample of urine is measured and creatinine

[illegible]

$$\text{Concentration index} = \frac{[illegible]}{5\ 7} = 220$$

$$\text{Filtration rate} = \frac{220\ 404}{60} = 147 \text{ cc per minute}$$

* An observation by C E Isaacs mentioned in Bieter s paper on this old American physiologist is a strong argument in favor of the existence of cilia

When we determine the filtration rate under these fairly standardized conditions we have found *in normal persons values between* 113 and 186 cc per minute. Values below 100 cc we regard as below normal. This test gives us information not about the state of the glomeruli but only *about their function*. *From this alone* we cannot say why filtration is decreased.*

The Functions of the Tubules and Tests for Them.—(*a*) The function *of the tubules is of a very complex nature and consequently* can be altered in different ways. The ability to reabsorb water may be decreased thus augmenting the urinary volume. A decreased ability *for reabsorption cannot however be demonstrated except* under conditions producing maximum concentration of the urine. This is done by the Volhard test by which the concentrating power *of the tubules is certainly best estimated*. *The simplest procedure* is to determine the maximum specific gravity obtained under the conditions of the test.

(*b*) *The reabsorption of the various threshold substances can* suffer—renal glucosuria is no doubt caused by insufficient reabsorption of sugar and we may find cases in which the reabsorption of *chlorine is altered so that chlorine in spite of a much too low*

normal. In these cases the regulation of the chloride reabsorption has failed.

(*c*) *As it is an important part* of the role of the tubules to keep the concentrated substances from diffusing back we can expect

increased backdiffusion

would mean that

with the urine is less

than should be expected at the concentration ratio of the urine. The percentage which is excreted—the excretion percentage as we have called it—is not however very constant even under normal conditions and changes in the excretion percentage must therefore be large before we can say definitely that the tubules are abnormally permeable.

One could expect perhaps that permeability might be increased for creatinine too, creatinine excretion then being no longer an index of filtration. This cannot be absolutely rejected but while we have met nothing which points toward such a possibility we have experiences which certainly point against it.

In urological cases where the ureter is obstructed we may find sometimes that the power of the diseased kidney to concentrate

* *In a series of normal children* Holten (193) has found the filtration to be on an average of 83 cc per min per sq m body surface with a minimum of 60 cc per min per sq m.

urea is practically abolished while creatinine is still concentrated almost normally.

The following case may serve as an example:

February 7. Ureter catheterization. On left side normal findings. Urine shows a concentration index of 200 while urea is concentrated 93 times. On right side the entrance of the catheter is stopped when 5 cm. in the ureter. Only very little urine obtained. Urine shows a concentration index of 177 *while urea is concentrated only 2.7 times.*

February 10. The stone is discharged.

February 14. Urine from left side shows a concentration index of 101, with urea concentrated 33 times. Right side urine has a concentration index of 120 while urea is concentrated 34 times.

When a case like this shows a practically normal degree of concentration of creatinine (177 against 200 on the normal side) while urea is decreased from 93 to 2.7 times we take this as indicating that the urea has diffused back through the walls of the dilated tubules while creatinine has done so only to a small extent. The finding is also interesting from a theoretical standpoint as an explanation of the secretion theory demands the assumption that increased pelvic pressure interferes with the function of the cells responsible for secretion of urea but not with those responsible for secretion of creatinine.

The determination of the excretion of those substances which are secreted by the tubules must be separately made. The substance of the greatest interest is ammonia. We have records of cases where the secretion of ammonia was ten times larger on one side than on the other.

The conclusion from these considerations is that it is impossible to find a single test which will answer the question of how the kidney functions in every respect.

SCHEME FOR TESTING THE FUNCTION OF A DISEASED KIDNEY

We suggest the testing of a diseased kidney in the following steps:

1. Testing of glomerular function by determination of filtration-rate.
2. Testing of tubular function:

(a) Concentrating power determined by the Volhard concentration test.

(b) Tightness of the tubules determined by comparison of urea excretion with creatinine excretion.

(c) Reabsorption of threshold bodies especially chloride by comparison of chloride excretion with chloride level of the blood plasma.

(d) Secretion of ammonia.

(e) Regulation of pH. This is an important function but how it is carried out is not quite clear—possibly both the reabsorbing

and secreting mechanism is concerned A number of cases have been studied but the theoretical significance of their disturbances is not yet elucidated

RESULTS OF CLINICAL STUDIES

By means of the tests outlined we have now studied a number of cases of which only a few shall be considered here In our classification of the disease we have followed Volhard and Fahr, with the exceptions that we have separated essential hypertension (cases without albuminuria) from nephrosclerosis and have separated amyloidosis from the other nephroses—this latter because the albuminuria is of another type and edema is often absent

Acute Nephritis —We have studied 6 cases from which we concluded that tubular function may sometimes be affected

Example *Case 5* —Clinical histo
Later vomiting Headache no co
October 31 entered the hospital
January 3 Blood pressure Octob
Volhard Strauss test December 10
1 010 February 17 specific gravity

TABLE 5

	Blood urea mg %	Filtration cc/min	Excretion percentage of urea
Nov 4	160	39	12 0
13	83	35	58 0
Dec 6	67	57	38 0
Jan 11	35	100	53 0
Feb 24	32	109	31 7

that even in these cases the tubular function may be involved—perhaps because the blood flow suffers through the anemia of the glomeruli Practically the whole supply of blood to the tubules passes through the glomeruli and any obstruction to the glomerular blood flow must involve disturbances in the blood supply of the tubules as well *

Chronic Glomerular Nephritis —We had 17 patients in this group 2 of whom were in the second stage (maximum specific gravity at least 1 020)
third (terminal) stage
rates varying from no
The clinical picture of the patients and the degree of reduction in filtration-rate bore a close correlation

* In a recent work Hou Jensen shows that at least about 97 per cent of all arterioles supplying the medulla of the kidney arise from vasa efferentia

Nephroses —We have classified as nephroses cases with edema but without increased blood pressure and without hematuria In this group we had patients showing normal or slightly reduced filtration values In 1 of them the reduction occurred during a short period when a large number of casts were being excreted Casts may block the tubules and in this way hinder the filtration One patient whom we regarded as having a nephrotic contracted kidney had a filtration rate of only 5 cc

Nephroses are good illustrations of the fact that a pathological change in an organ demonstrable histologically need not involve any functional change The most significant feature of the histological picture of nephrosis is the degeneration of the tubules though no change can be demonstrated in their function The glomeruli on the other hand are but slightly modified whereas the only functional change is the albuminuria which is undoubtedly of glomerular origin

Amyloidosis Four patients were observed with filtration rates from normal to 1 8 cc per minute or only one-eightieth of the normal value One case was followed closely

Albuminuria started July 1926 In May 1927 the filtration and blood urea were respectively 78 cc and 33 mg per cent October 1927 42 5 cc and 60 mg per cent January 1928 3 9 cc and 20? mg per cent The patient died in uremia

One other patient in this group also developed renal insufficiency In both nephrosis and amyloidosis renal insufficiency is seldom marked The comparative rarity of urinary symptoms in amyloidosis is because the patient usually dies from the underlying

heart symptoms In 1 case we observed a distinct influence of the state of the heart action on the filtration During an attack of arrhythmia the filtration was decreased to 6 8 cc whereas under the influence of digitalis the arrhythmia decreased while the filtration rose to 20 8 cc per minute

Essential Hypertension —In these cases (5 in all) which we distinguish from nephrosclerosis by absence of albuminuria we found normal values in 4 instances (from 117 to 176 cc) but in

and 121 cc respectively and the maximum concentration power to be 1 015 and 1 016 The other case showed the same concentration power with a filtration rate of 108 Both cases point to an isolated tubular dysfunction

Discussion of Symptoms —Following this brief review of our cases we wish to discuss a few of our findings of special interest together with some of the main symptoms of Bright s disease as elucidated by our material

Polyuria —We picture the mechanism bringing on polyuria as *follows When the filtration rate is considerably decreased* nitrogen retention in the blood begins The result is that the glomerular filtrate contains a much higher concentration of nitrogenous substances than usual so that even with normal tubules the concentration limiting the reabsorption of water is reached at an earlier stage Consequently a larger amount of fluid is left which cannot be reabsorbed a condition even more pronounced if the tubules are injured also The net result is that the concentration index of the urine is small and the excretion percentage of the backdiffusing substances is higher than it would be without the polyuria The polyuria however can hardly be considered a compensatory *mechanism of the kidney We may with Volhard call it an* obligatory polyuria

Hyposthenuria and Isosthenuria would be explained in the same way as decreased ability to reabsorb water

Attention is called to the fact that the isostenuria may be fully developed long before the filtration is reduced to the fatal limit When the Volhard test shows variations in specific gravity between 1 009 and 1 010 it fails to give any further indications about the progress of the disease Under these circumstances the filtration rate test will still be able to unveil an eventual downward course

a so
ble

Uremia (Nitrogen Retention) —In view of the fact that the degree of uremic symptoms and the nitrogen retention (urea retention) in the blood correspond closely *it may perhaps be inferred that* the cause of uremic symptoms is to be found in some nitrogenous substance

The degree of urea retention depends on the equilibrium between urea production and urea excretion The urea excretion is in most cases determined by the filtration rate of the kidney though in many cases the excretion percentage may be reduced so that it also contributes to the lowering of the excretion We therefore, find a very marked correlation between filtration rate and urea content of the blood As a rule we can say that as long as we have a filtration that is over 120 cc per minute we always find a blood

urea which is less than 40 mg per cent, with a filtration between 100 and 120 it may rise to 50 per cent. Serious urea retention does not occur until the filtration is decreased to about 60 cc per minute. It is very important to note that many cases with even a very low filtration rate show a normal blood urea, partly because of the compensatory action of the polyuria, partly because of low protein metabolism. Blood urea alone is not a good indicator of the state of the patient.

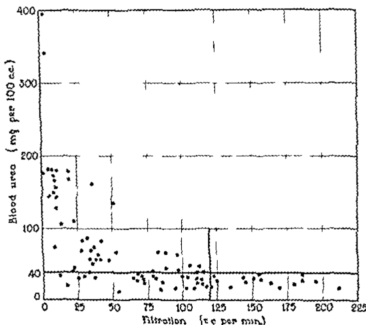


FIG. 10.—Relation between blood urea and filtration rate in persons with and without kidney disease. Observe the number of cases in which the blood urea is normal while the filtration rate is low. (Holten and Rehberg, Acta med. Scand.)

The determination of the filtration rate has a high prognostic value in these cases, as it allows one to determine the seriousness of an elevated blood urea. A blood urea of 150 mg is much more serious with a filtration of 10 cc per minute than it is if the filtration is 60 cc per minute. In the latter case it is almost certain that diet combined with a polyuria provoked by the ingestion of large amounts of water will be able to reduce the blood urea to a normal value. As a rule, we can say that when the filtration

In the begi[illegible]
No edema [illegible]
100 cc Volh[illegible]
gravity, 1 005
Blood urea, 80 mg per cent Diuresis, 1500 to 2000 cc

He was put on a diet of fat and carbohydrate with only 40 gm of protein and receives, moreover, about 200 cc. extra fluid daily, thus maintaining a diuresis of about 3500 cc. In this way he has been kept in working condition as a teacher for two years. The filtration tests have shown the following·

TABLE 6

Date	Filtration cc per min	Blood urea mg per cent
Oct 20 1928	41	73
Dec 5 1928	37	75
Feb 1 1929	36	71
Mar 13 1929	26	85
May 12 1929	37	86

The exacerbation in the state of the patient shown by the filtration and by the blood urea on March 13 was due doubtless to the fact [illegible] a strenuous character [illegible] water-drinking [illegible] filtration-rate in any [illegible] he filtration test with those from the Volhard concentration test we believe we obtain a better picture of the state of the kidneys than was previously possible We are able to follow closely variations in the degree of the disease and are often enabled to draw conclusions both with regard to prognosis and with regard to therapeutics

The [illegible] the pro[illegible] has come for a [illegible] hypothesis in

REFERENCES

1 BIETER, R N 1929 Charles Edward Isaacs, Ann Med Hist, n s, 1, 363-377
2 CUSHNY, A R 1926 The Secretion of Urine, 2d ed, London, Longmans, Green & Co (1st ed, 1917)
3 FOLLING, A 1929 On the mechanism of the ammonium chloride acidosis Acta med Scand vol 71
[illegible] function on
[illegible] pathological
[illegible] e, Acta med
6 HOU-JENSEN 1929 [illegible] in der Niere des Menschen, Berlin, Julius Springer

7 Höber R 1930 Ueber die Harnbildung in der Froschniere XIX Mitteilung Pfluger s Arch 224 422–440
8 ——— 1932 Ueber die Kreatininausscheidung durch die Froschniere Pflüger s Arch 230 327 330

J 20 401–45.
19 Rehberg P Brandt and Blem C 1937 Ueber das Harnstoffdepot der Froschniere und seine Bedeutung fur den Excretions-mechanismus Pfluger s Arch 230 689–696
20 ——— 1932 Weitere Untersuchungen uber das Harnstoffdepot der Niere Pfluger s Arch 230 697 704
21 Richards A N 1929 Methods and results of direct investigations

CHAPTER V

THE EXCRETION OF THE NON-METABOLIZED SUGARS IN THE DOGFISH, THE DOG AND MAN

By HOMER W SMITH, Sc D

Introduction —A substance suitable for measuring glomerular filtration must obviously be completely filtrable from the plasma, it must be physiologically inert, at least so far as renal function is concerned and readily amenable to quantitative determination in both plasma and urine In addition, it must be neither secreted nor reabsorbed by the renal tubules ureters and bladder Of these several criteria the most difficult to establish as universally valid are those concerning secretion and reabsorption

In seeking a substance fulfilling these requirements the author was led to the investigation of the non metabolized sugars by Marshall and Grafflin's[18 19 20] observation that glucose is excreted in the urine by glomerular but not by aglomerular fishes On broad principles the author related this circumstance to the fact that, being a food and not a waste product, glucose has been conserved by the vertebrates throughout their evolution, and at no time continuously rejected from the body The excretory organs have never been called upon, therefore, to secrete this substance, and were possibly incapable of doing so The appearance of glucose in the urine of glomerular animals during hyperglycemia or phlorizin poisoning was in this view referable to the incomplete tubular reabsorption of this substance from the glomerular filtrate (The circumstance of filtration and subsequent reabsorption of glucose or other substances is apparently one that owes its origin to the course of evolution of the glomerular vertebrate kidney—Smith[35 36]) Because it is normally reabsorbed by the tubules, glucose itself is not suitable for the evaluation of glomerular filtration, and although this reabsorption can be arrested by phlorizin there is no reason to believe that other physiological activities of th[illegible] the

us

the

tubules other sugars might not be secreted by them, and that, among the metabolically inert sugars one or more might be found that were not reabsorbed as was this physiologically important

fuelstuff Consequently, investigations were undertaken in this laboratory on the excretion of non-metabolized sugars, xylose[4–7, 23, 24] and sucrose [7, 17, 21, 22]

Since conclusions drawn from a single species must be viewed with some uncertainty, these investigations have been extended to include the dogfish, the dog and man as fair extremes of the chordate phylum

THE EXCRETION OF NON-METABOLIZED SUGARS BY THE DOGFISH

The dogfish, Squalus acanthias, was chosen for the practical [illegible] the Elasmobranch fishes for the purpose of maintaining the osmotic pressure of the blood (Smith[33, 34, 36]) That the failure of the elasmobranch kidney to excrete this freely diffusible substance is the result of active conservation (tubular reabsorption) is indicated by the fact that during diuresis and under other circumstances the urea concentration in the urine rises and approaches that of the blood

The earlier experiments of Clark and Smith[3] showed that xylose was copiously excreted by the kidney of this animal The administration of phlorizin immediately induced an excretion of glucose (as it does in all vertebrates so far examined) to such an extent that the glucose clearance approximated the xylose clearance, although the xylose clearance was not increased More recent experiments by Shannon[29] furnish additional evidence on this point In Table 7 there are given simultaneous clearances (in the phlorizinized dogfish) of glucose and xylose on the one hand and of glucose and sucrose on the other, as well as the simultaneous clearances of xylose and sucrose in the normal animal Xylose and sucrose (the latter after parenteral administration, of course) are handled as [illegible] by aglomerular fish (Opsanus tau and Lophius piscatorius), while not even traces of sucrose diffuse across the tubules of Lophius In two unpublished experiments of Clarke's, the plasma, after the intravenous injection of sucrose, contained 540 and 1060 mg per cent, respectively, of this substance Urine collected over the following four-hour period had less than 1 mg per cent of sucrose

in it Not only does this show that sucrose is not secreted by the aglomerular tubule of Lophius, but that diffusion of this substance across the tubule from the blood to the urine is so small as to be entirely negligible As between two fish, the inability of the aglomerular kidney to secrete xylose and sucrose would argue strongly for a similar inability in the glomerular kidney, but to support this inference there is the observation of Marshall and Grafflin,[20] that glucose disappears entirely from the urine of the glomerular sculpin when the glomeruli are closed by large doses of phlorizin

TABLE 7—COMPARISON OF THE GLUCOSE XYLOSE AND SUCROSE CLEARANCES IN PHLORIZINIZED DOGFISH AND XYLOSE AND SUCROSE CLEARANCES IN NORMAL DOGFISH *

Experiment No	Total concurrent time hrs	Urine volume cc /kg / day	Glucose		Xylose		Clearance cc /kg /day		Ratio
			Plasma mg per 100 cc	Urine mg per 100 cc	Plasma mg per 100 cc	Urine mg per 100 cc	Glucose	Xylose	
53	33	44.0	83	129	210	320	68.6	66.9	1.03
	45	32.0	80	136	174	289	54.4	53.1	1.03
	57	28.0	78	136	150	256	49.0	48.0	1.02
55	33	46.2	116	201	140	244	80.0	80.4	0.99
	45	37.5	110	198	123	234	67.5	71.2	0.95
	57	26.0	103	252	109	272	64.0	65.3	0.98
					Sucrose			Sucrose	
3	21	38.0	231	531	193	454	87.5	89.3	1.02
	23	34.7	218	545	170	421	86.8	86.1	1.01
	26	26.6	214	652	167	593	80.8	83.3	1.03
	28	18.7	212	727	153	497	64.1	60.8	0.95
	32	24.7	211	670	145	436	78.3	74.4	0.95
4	21	46.9	248	433	306	497	82.1	76.0	0.93
	23	35.7	194	447	267	583	82.1	77.8	0.95
	26	25.8	181	448	254	637	64.0	64.4	1.01
	28	27.2	172	432	243	638	68.3	71.3	1.04
	32	36.0	162	345	232	475	76.6	73.8	0.96
			Xylose				Xylose		
1	23	8.9	148	612	356	1632	36.8	37.6	1.02
	26	12.2	132	511	363	1431	47.3	48.1	1.02
2	23	7.2	162	822	370	1767	36.5	34.4	0.94
	26	7.6	148	718	364	1705	36.9	35.7	0.97

* Summaries of these experiments are given by Shannon [29]

The above evidence is wholly consonant with the supposition that glucose, xylose and sucrose are excreted exclusively by glomerular filtration, xylose and sucrose passing down the lumen of the tubules, where the glucose is actively reabsorbed, except in the phlorizinized animal where its reabsorption is partially or completely blocked

... the reabsorp-
reabsorp-
... will be

eatinine
in the mammal, but
...ously secreted by the
... for this
purpose is open to a ... of the
fact that there is no evidence of its exclusive ... nimal

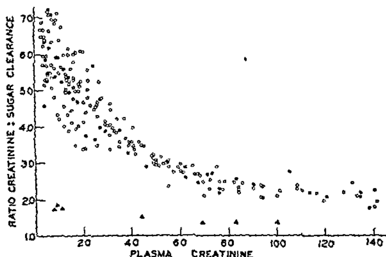


Fig. 11 The ratios of the creatinine clearance to the xylose or sucrose clearances ... plotted against the observed plasma level of creatinine in the dogfish. Creatin... ... as open circles. Creatinine sucrose ratios are shown as ... are shown as solid triangles ... scattering

so far studied. The experime... ...d Shannon[23] show that the creatinine clearance in the dogfish normally greatly in excess of the clearance of the non metabolized sugars while in the phlorizinized dogfish the creatinine clearance falls and approaches the xylose (or glucose) clearance. These results indicate that creatinine is secreted in this animal under normal conditions and that this secretion is impaired by phlorizin. As further evidence in this direction Shannon has shown in the normal dogfish that the creatinine clearance is greater when the plasma concentration of this substance is low than when the plasma concentration is high: at plasma levels below 7.5 mg per cent the creatinine clearance averages 5.8 times the xylose or sucrose clearance and

as the plasma level is raised to higher values the creatinine clearance falls and approaches the xylose clearance asymptotically (see Marshall and Grafflin[20] for the initial observations on this point) The full import of Shannon s experiments is conveyed effectively by Fig 11, compounded of data from several dogfish

The rate of excretion of a non reabsorbed substance excreted exclusively by filtration all other factors remaining constant must increase in direct proportion to the plasma level that is the clearance will be independent of the plasma level No explanation is evident for the observed curvilinear relationship in the dogfish between creatinine clearance and plasma level other than secretion and Shannon s analysis of his results suggests that the fraction of creatinine cleared from the plasma over and above filtration is such that a constant amount of energy would be necessary to accomplish the secretion of this substance Though the problem cannot be approached thermodynamically at the present time the evidence is such as to be readily reconciled with the apparent secretion of a considerable quantity of creatinine by the tubules in addition to that which is filtered and to be unreconcilable with an exclusive process of filtration

The fact that phlorizin depresses the creatinine clearance from a level six times as great as the xylose clearance to a level less than twice as great without raising the absolute value of the xylose clearance itself indicates that the excretion of creatinine is effected by some unstable and easily injured mechanism It is not evident how phlorizin could impair the glomerular excretion of creatinine nor is there anything to support the belief that this drug would stimulate a suppositious reabsorption of creatinine while blocking the accepted reabsorption of glucose and leave a suppositious absorption of xylose and sucrose unchanged

All the evidence from the dogfish then points to the belief that creatinine is excreted in part by tubular secretion and in part by glomerular filtration while xylose and sucrose are excreted exclusively by the latter route without the reabsorptive process that is normally present for glucose

THE EXCRETION OF NON-METABOLIZED SUGARS BY THE DOG

The dog appears to resemble man more closely in respect to renal function than any other animal on which extensive information is available at the present time For this reason the dog has been chosen as the principal experimental animal in the study of mammals The data given in Table 8 are representative of the results obtained in the laboratory of the Department of Physiology of the New York University and Bellevue Hospital Medical

TABLE 8.—COMPARISON OF XYLOSE AND SUCROSE CLEARANCES IN NORMAL DOG

Experiment No.	Total concurrent time min.	Urine volume cc./min.	Xylose: Plasma mg. per 100 cc.	Xylose: Urine mg. per 100 cc.	Sucrose: Plasma mg. per 100 cc.	Sucrose: Urine mg. per 100 cc.	Clearance cc./sq. m./min.: Xylose	Clearance cc./sq. m./min.: Sucrose	Sucrose / Xylose
			(From Jolliffe, Shannon and Smith[11])						
85	32	1.08	98.1	1652	109.2	1880	33.7	34.4	1.02
	60	1.00	106.4	2019	102.4	2116	38.3	41.7	1.09
	90	1.03	116.4	2086	115.2	2308	34.2	38.2	1.12
86	31	1.03	95.8	4025	104.8	4075	57.0	52.7	0.92
	60	1.17	105.2	4130	108.8	4398	60.6	63.2	1.03
	92	1.22	101.3	3820	109.1	4210	60.6	62.0	1.02
			(From Jolliffe, Shannon and Smith[2])						
120	22	3.63	136.0	3410	111.0	2885	119.7	124.1	0.97
	43	3.91	136.0	2986	106.0	[illegible]88	112.9	111.0	1.02
	60	4.47	136.0	255[illegible]	101.0	1926	110.4	109.0	1.01
146	20	2.05	212.0	3400	208.0	3270	35.8	35.0	1.02
	59	2.20	219.0	3625	216.0	4080	39.6	39.7	1.00
	79	2.10	178.0	3355	256.0	4850	43.0	43.3	0.99
					(From Pitts[8])				
82	10	2.55	144.0	835	133.0	765	20.7	20.6	1.00
	21	1.82	139.0	960	145.0	1010	22.9	23.0	1.00
	33	1.25	128.0	1130	151.0	1315	20.1	19.8	0.99
83	10	6.40	186.0	1090	122.0	735	75.0	77.0	1.03
	21	4.76	171.0	1370	112.0	875	76.2	74.4	0.98
	31	3.62	157.0	1725	105.0	1170	79.6	80.8	1.01
				(From Shannon, unpublished.)					
214	13	4.69	112.0	1095	239.0	2335	63.8	63.6	1.00
	26	5.62	117.0	842	259.0	2000	56.2	60.0	1.07
	39	6.8[illegible]	121.0	859	273.0	2000	67.2	69.4	1.03
217	10	5.90	123.0	724	184.0	1070	43.0	41.8	0.97
	21	6.00	128.0	731	192.0	1113	41.8	42.4	1.01
	32	6.51	130.0	680	215.0	1115	41.7	41.3	0.99
218	10	3.50	127.0	886	153.0	1000	32.1	30.1	0.94
	21	3.28	128.0	919	172.0	1170	30.0	23.3	0.95
	31	3.30	130.0	982	189.0	1365	32.7	31.4	0.96
212*	10	6.00	116.0	1095	262.0	2840	65.8	75.6	1.15
	21	7.33	122.0	888	273.0	[illegible]	62.0	75.6	1.22
	31	5.80	126.0	1199	274.0	3000	64.2	76.0	1.18

* Delivered of pups two days after this experiment.

College and show that in the normal dog the simultaneous clearances of xylose and sucrose are identical within the limits of experimental error in the determination of the sugars. In experiments with phlorizinized dogs the trisaccharide, raffinose, shows the same clearance as glucose (Jolliffe, Shannon and Smith[11]), since

xylose, sucrose and glucose give identical clearances under these same conditions it appears that these sugars are all handled in the same manner by the kidney

The question of whether or not phlorizin completely blocks the *active reabsorption of glucose* is not open to direct investigation, but evidence bearing upon it can be obtained from the behavior of the various substances studied The administration of phlorizin sometimes leads to a drop in the absolute *xylose clearance, for* unexplained reasons It is a well-known fact that the urea clearance is characteristically inconstant, both in the dog[11 13 14] and in man, and we may tentatively ascribe this to variations in blood flow, glomerular pressure etc It has been observed that the xylose clearance is equally variable in the normal dog,[17 30] and it is not unwarranted [illegible] lorizin *produces transient* [illegible] is significant however, [illegible] does phlorizin cause a rise in xylose clearance, and this fact in itself would indicate that there is no extensive reabsorption of xylose that is blocked by phlorizin It might be that a drop in glomerular [illegible]

for the measurement of glomerular filtration that can be placed definitely on independent grounds beyond the influence of this drug *But it is significant that the simultaneous xylose and urea* clearance maintain a fairly constant ratio both in the dog[12 30 31] and in man[2 10] and it is the exception rather than the rule for phlorizin to cause the xylose clearance to rise relative to the urea clearance Since it is unlikely that phlorizin blocks the reabsorption of urea and xylose to precisely the same extent, and at the same time reduces the true glomerular clearance to the same degree (*thus keeping the total clearance constant*) *it appears that there is* no reabsorption of xylose that is blocked by this drug *

It may be noted that second and massive injections of phlorizin do not increase the excretion of glucose over the rate obtained by a minimum effective dose and on this *prima facie* evidence it is difficult to believe that the drug blocks the reabsorption of part of the filtered glucose and fails to block the reabsorption of the rest But admitting the possibility it is then necessary, *in order to* [illegible]

the xylose, sucrose and glucose clearances are identical within a

* Work completed in this laboratory since the preparation of this paper has led the author to question this point The reader is referred to the note appended to the end

margin of a few per cent In view of the way these several sugars are handled in the normal animal this reasoning appears to us to be futilely circumlocutionary

[illegible] these sugars by [illegible] matter can be [illegible] to consider the anatomy of the kidney Practically all physiologists have agreed that the structure of the glomerulus is such as to promote easy diffusion and therefore easy filtration The corollary is this anatomical interpretation is that the structure of the tubule of such as to restrict diffusion and therefore to permit the specific operation of reabsorption (or secretion) To overlook this fact is to disregard the one fundamental contribution that anatomy can make to this subject

It is more to the point perhaps to recall that not even traces of sucrose diffuse from the blood through the tubules of the aglomerular fish to appear in the urine It is an improbable assumption then to suppose that these sugars diffuse in the reverse direction that is from the urine into the blood in either the fish or the dog Diffusion in the proper meaning of the word must occur with equal facility in either direction or it ceases to be diffusion and becomes active reabsorption mediated either chemically or by a Maxwell demon

But still more immediately the U P ratio of urea in the dog may reach values of 300 (Ralli Brown and Pariente[7]) or higher and this substance is one of the most diffusible known In view of the fact that such high concentration gradients of urea can be effected by the dog kidney it is *a priori* unlikely that the tubules are very permeable in the proper sense to substances like glucose xylose and sucrose But with the view of securing more certain evidence Jolliffe Shannon and Smith[11] chose three sugars differing widely in molecular weight and therefore in diffusibility for their experiments in the dog Finding no significant difference in the clearances of xylose (m w = 150) sucrose (m w = 342) and raffinose (m w = 504) and with only a 30 per cent discrepancy between the clearance of urea (m w = 60) on the one hand and the clearances of these three sugars on the other they were convinced that there [illegible]

[illegible] gated In the diseased kidney or in the normal kidney at very low urine flows where there is a correspondingly high U P ratio it may be that there is some small backdiffusion of sucrose or xylose The problem can hardly be investigated with confidence until some substance of large molecular weight and still lower diffusibility, which checks xylose and sucrose at high urine flows is available)

xyl
Jol
in the dog (1 3 to 1 5) than in the dogfish (4 2 to 7 2) due in part perhaps to intrinsically greater secretory capacity in the latter but it must also be noted that the fish tubules receive a copious supply of venous blood by way of the renal portal system that does not reach the glomeruli and that is therefore not available for filtration The creatinine clearance in the normal dog is suffi ciently above the xylose and sucrose clearance however to indicate that creatinine is removed from the blood by tubular secretion as well as by filtration

A curvilinear relationship between the creatinine clearance and the plasma level of this substance has not been demonstrated in the dog (Shannon Jolliffe and Smith[31]) but to date the creatinine clearance has been studied at relatively narrow plasma-creatinine levels and such a relationship cannot be definitely excluded at this time

TABLE 9—COMPARISON OF GLUCOSE XYLOSE AND CREATININE CLEARANCES n DOG BEFORE AND AFTER PHLORIZIN

Experiment No	To al oncu rent t me	Ur ne volume cc /m n	Xylose		Glucose		Creat n ne		Clearances cc /sq m /min			Ratios	
			Plasma mg per 100 cc	Ur ne mg per 100 cc	Plasma mg per 100 cc	Urine mg per 100 c	Plasma mg per 100 cc	Ur ne mg per 100 cc	Xylose	Glu ose	C ea nne	Glu ose / Xylose	C eat / Xylose
				(F	om Shanno	n Jolli	ffe and	Sm t	h.[a])				
160	0	3 50	188	272	77	0 0	24 4	412	59 4	0 0	8? 0	0 0	1 38
	49	7 62	19	3000	78	0 0	2 0	457	56 8	0 0	75 5	0 0	1 33
	76	2 73	177	2886	76	0 0	19 5	390	61 8	0 0	75 8	0 0	1 23
										A	er	0 0	1 32
				After	phlori	z n (40	0 mg	kg					
	106	2 63	145	2150		1158	17 5	273	54 2		58 9		1 05
	135	2 34	115	2069	89	1574	15 6	278	58 4	59 4	57 9	1 0	0 99
	16_	2 14	87	1800	76	1535	13 9	288	61 6	60 3	61 6	0 98	1 00
										A	er	1 00	1 01
				, —				50 mg /kg					
?1	10												
	21												
	31												
	42												
	61												
	8												
				After	phlor	z n (40	0 mg /	kg)					
75	10	4 95	88	791	79	786	23 0	211	73 3	81 ?	74 4	1 11	1 0
	18	4 65	85	841	85	918	2 6	222	75 0	82 0	74 9	1 09	1 00
	30	4 83	81	823	90	1029	21 9	225	80 8	91 0	81 3	1 12	1 01
										A	e	1 11	1 01

The supposedly secretory nature of the excess creatinine clearance in the dog is confirmed by the action of phlorizin Data on the effect of phlorizin on the glucose and creatinine clearances are given

in Table 9 The administration of this drug temporarily reduces the creatinine clearance to the xylose or sucrose clearance, even while it brings the glucose clearance up to the same level (Shannon, Jolliffe and Smith [31] Pitts[26])

Further evidence on the matter of glomerular filtration in the dog is furnished by the observations of Pitts[26] on the excretion of inorganic phosphates after intravenous injection The phosphate

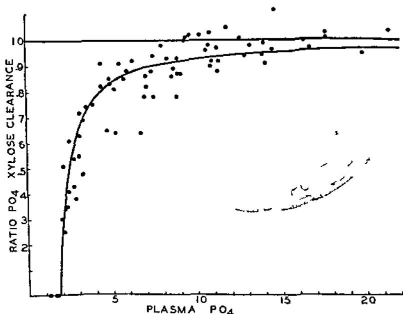


Fig 12 —The ratios of the phosphate clearance to the xylose clearance are plotted

this time

clearance rises as the plasma level rises, and approaches the xylose or sucrose clearance without ever exceeding the latter (Fig 12) Apparently some definite amount of phosphate (related perhaps, to the plasma and urine concentrations) is reabsorbed from the glomerular filtrate by the tubules, this moiety exerts less and less

clearance so that the latter no longer bears its natural relationship to the plasma level (White and Monaghan [37] Pitts[26]) but even in the presence of phosphate the drug continues to bring the glucose clearance up to and the creatinine clearances down to the level of the xylose clearance (Pitts[26]) It is apparently the excretion of phosphate that is affected and not the excretion of the other substances

White and Monaghan[35] have failed to observe the above identity with respect to
to creatinine in
these experimen
discrepancies between the results obtained in the St Louis laboratory and the author s In only 2 dogs have highly discrepant ratios between the apparent xylose and sucrose clearances been obtained a result that may have been influenced by the presence of lactose in the blood and urine (for example see Experiment 212 Table 6) Otherwise the results confirm the original conclusions of Jolliffe Shannon and Smith [11] In no case has the creatinine clearance failed to approximate the clearance of the non metabolized sugars or glucose after adequate doses (100 mg per kg) of phlorizin Lack of space prohibits a discussion of the possible reasons for the conflicting results obtained by White and Monaghan and the investigators in this laboratory (See Pitts *Am J Physiol* 542 109 1934)

THE EXCRETION OF NON METABOLIZED SUGARS BY MAN

Keith Power and Peterson [5] have examined the excretion of sulphate urea sucrose and creatinine in normal man and find average clearance values of 35 50 100 and 140 to ?00 respectively More recently these same investigators have examined the simultaneous clearances of xylose and sucrose in normal man and find that the former averages 10 5 per cent lower than the sucrose clearance [16] These investigators remark Although the differences were not greater than might be expected from analytical errors it seems improbable that such errors would fall uniformly in one direction In spite of this it must be concluded that these sugars are excreted by the kidney in a similar manner

Similar comparisons of xylose and sucrose have recently been made at Bellevue Hospital by Dr Herbert Chasis the results of which are published for the first time in Table 10 The author is indebted to Dr Chasis for permission to include them here When due allowance is made for probable sources of error the relatively low plasma xylose superimposed on naturally occurring non
of an ascending plasma
asma sucrose curve with
A I difference of these
substances and the not inconsiderable difficulties attending the

analysis of mixtures of two foreign sugars in the presence of glucose —the results of these experiments may be accepted as evidence of the essential equivalence of the simultaneous xylose and sucrose clearance in normal man The fact that in these experiments the sucrose xylose ratio is greater than 1 is not evidence in the author s opinion that these sugars are handled differently as White and

TABLE 10 —COMPARISON OF XYLOSE AND SUCROSE CLEARANCES IN NORMAL MEN UNPUBLISHED EXPERIMENTS OF DR HERBERT CHASIS *

Subject	Surface area sq m	Total concurrent time min	Urine volume cc min	Xylose: Plasma mg per 100	Xylose: Urine mg per 100 cc	Sucrose: Plasma mg per 100	Sucrose: Urine mg per 100	Clearance cc /sq m min: Xylose	Clearance cc /sq m min: Sucrose	Ratio
C R ♀	1 53	18	4 00	67 4	1127	363	6053	43 7	47 8	1 09
		38	4 00	71 1	1475	303	6849	54 0	59 0	1 09
		59	3 90	7[illegible] 2	1 08	253	4306	47 6	44 0	1 03
		83	3 46	77 4	1730	196	4695	50 6	54 0	1 07
M B ♀	1 36	21	4 [illegible]0	37 9	595	4[illegible]4	7201	48 5	5[illegible] 4	1 05
		36	3 97	36 0	670	370	6600	46	51 8	1 1[illegible]
		5[illegible]	3 00	34 5	617	334	6460	39 4	42 6	1 08
		71	2 68	3[illegible] 6	711	[illegible]90	[illegible]0[illegible]4	4[illegible] 9	47 7	1 11
H O ♂	1 8[illegible]	[illegible]0	6 31	60 4	1008	[illegible]31	40[illegible]5	57 8	60 4	1 05
		40	6 [illegible]0	60 1	1046	[illegible]01	3903	60 2	66 [illegible]	1 10
		59	5 [illegible]	59 8	10[illegible]4	1[illegible]9	314[illegible]	55 6	57 0	1 03
								Aver		(1 08)

* From the Department of Physiology New York University and Bellevue Hospital Medical College and the Third Medical Division Bellevue Hospital

Chasis Jolliffe and Smith[9] have shown that single intravenous doses of phlorizin of adequate size raise the glucose clearance in man to the level of the xylose and sucrose clearance data from their experiments are included in Tables 11 and 12 Once the reabsorption of glucose is completely blocked the simultaneous glucose xylose and sucrose clearances remain identical within experimental error regardless of how much phlorizin is given (between the limits of 12 and 60 mg per kg) In view of this fact and in view of the further facts that the xylose clearance is not raised significantly in respect to the simultaneous urea clearance nor in respect to its own control level by the administration of phlorizin it appears that in man as in the dog and the dogfish xylose and sucrose are neither secreted nor reabsorbed

TABLE 11 —COMPARISON OF XYLOSE GLUCOSE UREA AND CREATININE CLEARANCES IN MAN FOLLOWING INTRAVENOUS ADMINISTRATION OF PHLORIZIN [1]

Subject	Phlorizin mg per kilo	Surface area sq m	Total concurrent time min	Urine flow per min cc	Clearances cc /sq m /min				Creatinine / Xylose	Urea / Xylose	Glucose / Xylose
					Xylose	Glucose	Creatinine	Urea			
M M	6 07	1 52	31	3 20	18 4		43 2	14 5	2 35	0 79	
♀			63	3 20	34 3		78 5	26 5	2 29	0 77	
			90	Washout period							
			121	2 60	30 8	31 0	65 1	26 8	2 11	0 87	1 01
			150	3 60	37 6	34 6	86 4	32 5	2 30	0 86	0 92*
			179	3 10	36 5	15 3	83 2	30 2	2 28	0 83	0 42*
A H	11 80	1 27	18	12 70	58 0		106 7	44 0	1 84	0 76	
♀			74	Washout period							
			94	3 20	49 1	50 3	86 2	38 8	1 76	0 79	1 02
			114	3 10	52 2	55 2	93 6	40 3	1 79	0 77	1 06
			139	2 90	55 4	57 6	94 0	40 8	1 70	0 74	1 04
M S	15 70	1 39	25	1 60	53 5		96 3	41 7	1 80	0 78	
♀			72	Washout period							
			90	1 67	43 9	45 4	75 5	31 0	1 72	0 71	1 03
			104	1 63	42 3	44 2	73 0	30 7	1 73	0 73	1 04
			130	1 75	48 6	48 3	81 2	34 3	1 67	0 71	0 99
C S	20 40	1 47	21	7 30	58 6		109 5	34 3	1 87	0 58	
♀			41	2 60	60 8		112 3	35 4	1 85	0 58	
			74	Washout period							
			94	2 37	52 4	54 0	105 5	30 6	2 01	0 58	1 03
			115	2 25	55 4	56 0	108 5	33 1	1 96	0 60	1 01
			139	2 26	58 0	56 8	110 9	34 9	1 91	0 60	0 98
N O	65 20	1 60	20	9 70	43 0		76 3	33 1	1 77	0 77	
♀			44	6 62	41 4		82 5	34 3	1 99	0 83	
			91	Washout period							
			106	2 08	30 8	33 4	46 3	20 0	1 50	0 65	1 08
			126	2 10	32 9	34 3	49 9	20 7	1 52	0 63	1 04
			145	1 94	30 2	32 6	48 6	19 4	1 61	0 64	1 08

* Incompletely phlorizinized

TABLE 12 —COMPARISON OF XYLOSE SUCROSE AND GLUCOSE CLEARANCES IN MAN FOLLOWING INTRAVENOUS ADMINISTRATION OF PHLORIZIN [2]

Subject	Phlorizin mg per kg	Surface area sq m	Total concurrent time min	Urine flow per min cc	Clearances cc /sq m /min			Glucose / Xylose	Sucrose / Xylose
					Xylose	Glucose	Sucrose		
F M	29 7	1 32	19	4 30	55 7	50 9	53 8	0 91	0 97
♀			39	3 95	55 4	55 4	53 6	1 00	0 97
			64	3 48	53 3	54 1	54 3	1 02	1 02
V T	41 9	1 59	31	4 90	46 8	41 0	45 0	0 88	0 96
♀			51	3 80	37 8	34 7	35 6	0 92	0 94
			75	5 79	48 4	45 5	48 4	0 94	1 00
W M	45 3	1 49	20	4 02	42 0	39 8	42 0	0 95	1 00
♂			43	3 97	47 0	45 9	46 1	0 98	0 98
			66	4 09	49 5	48 1	50 0	0 97	1 01
			87	3 77	47 8	48 1	47 4	1 01	0 99
F M	59 4	1 32	29	4 30	55 1	56 0	58 6	1 02	1 06
♀			54	3 56	57 2	57 7	61 4	1 01	1 07
			82	2 86	46 2	44 8	48 5	0 97	1 05
			104	2 18	44 3	44 0	45 7	0 99	1 03

TABLE 13.—COMPARISON OF XYLOSE, UREA AND CREATININE CLEARANCES IN NORMAL MEN. SUMMARIES OF THESE DATA HAVE BEEN PUBLISHED BY JOLLIFFE AND CHASIS[16]

Subject	Surface area sq m	Urine volume cc per min	Xylose: Plasma mg per 100 cc	Xylose: Urine mg per 100 cc	Urea: Plasma mg per 100 cc	Urea: Urine mg per 100 cc	Creatinine: Plasma mg per 100 cc	Creatinine: Urine mg per 100 cc	Clearances cc per min: Xylose	Clearances: Urea	Clearances: Creatinine	Ratios: Creat/Xylose	Ratios: Urea/Xylose
J S	1.73	5	7 6	3330.0	23.6	8 3 0	5.2	460.0	64.7	50.7	110.2	1.84	0.8
								Aver	64.7	50.7	110.2	1.84	0.78
K S	1.04	1	8.0	4295.0	40.3	13 0	5.5	84 0	48.5	31.5	111.9	2.30	0.6
								Aver	48.5	31.5	111.9	2.30	0.6
F M	1.6	1	93.0	3675.0	33.8	883.0	9.7	5 8.0	47.2	30.5	73.5	1.56	0.6
		1	86	3 0	33.8	827.0	9.9	546.0	44.1	23.2	65.4	1.45	0.56
		0	0	3 60.0	33.8	802.0	9.9	6 0	5 .2	33.4	0.8	1.53	0.64
								Aver	47.8	31.0	72.9	1	0.65
B J	1.80	2	42.0	2100.0	17.7	616.0	7.0	448.0	6 5	41.8	83.3	1.34	0.67
		1 8	41.0	23 0.0	17.7	728.0	7.4	606.0	57.5	41.5	82.8	1.43	0.72
			35.0	45.0	17.7	696.0	3	58 0	67.3	46.0	94.0	1.40	0.68
								Aver	6 4	43.5	86.7	1.35	0.65
C K	8	2 8	30.0	1 0.0	4.0	804.0	9.9	7 0	73	51.9	112.5	1.41	0.65
		2	24.0	1 0.0	4.0	8 0	9.4	700	75.7	50.7	103.5	1.37	0.6
		2 4	21	14 0.0	21.0	1 0	9.0	6 8 0	7 0	0.0	100	1.27	0.63
								Aver	7 2	0 8	10 5	1 3	0.6
M I	76	11 8	47	433.0	8.5	3 0	7.5	158.0	58.3	44.9	141.0	2.4	0.77
			46.0	78.0	4.0	760.0	7.5	5 0	5 3	45.2	120.0	2.3	0.86
		6	41.6	43.0	0	7 0	7.4	281.0	61.7	54.2	131.0	2.1	0.87
								Aver	5 4	48.1	131.0	2.3	0.84
S T	81	8	7.0	f	7.7	188.5	8.8	160.0	46.7	31.1	83.1	1.78	0.66
		7 3	37.0	34 3	27.6	1 0 8	9.8	148.0	34.3	2 5	61.1	1.64	0.68
								Aver	42.5	28.3	72.1	1.6	0.66
I I	2.10	7 6	3.0	41.0	23.6	188.0	1.0	313 0	43	28.8	73.1	1.6	0.66
		3 3	2.0	9 2	24.0	0	14	0.0	49.5	35.1	87.1	1.6	0.71
		4 2	24.8	0	4.1	800.0	11.0	450.0	44.8	9 9	80.5	1.78	0.67
								Aver	45.9	31.3	80.2	1.74	0.68
A R	1.8	9 3	34	2 7	3.6	179.9	11.2	17 5	42.2	27.4	77.5	1.81	0.6
		2 7	1.5	8 5	32.1	5 6 1	10.5	555.0	40.4	25.9	76.2	1.88	0.61
		1	2.3	1 60.0	31.7	914.0	10.2	81 0	46.9	30.3	83.8	1.73	0.6
								Aver	43.2	27.6	73.2	1.63	0.65
C C	1.77	10	43.5	4 0.0	33.7	275.0	5.0	84.2	57.0	39.8	99.2	1.74	0.0
		9 0	4.3	45.0	3.7	37	4.9	87.2	51.4	37.1	91.7	1.76	0.7
		6	4.1	734.0	31.4	372.5	4.7	133.0	59.1	37	93.9	1.81	0.72
								Aver	53.5	38.1	94.9	1.77	0.71
J K	1.7	1	37.1	1 14	33.8	1091.7	11.6	90.0	43.6	31.7	85.0	1.71	0.0
		1	31.2	1748.3	33.6	11 5.5	11.1	108.0	43.0	31.2	86.1	1.75	0.70
		14 6	41.0	8.0	33.1	141.0	2.4	23.3	0	35.1	80.8	1.55	0.68
		18 5	33	2 0.0	32.5	1 7.5	2.5	8	53.6	38.6	88.2	1.61	0.68
		16 2	43.0	6.0	31.8	128.5	2.5	24.2	55.8	37.1	87.7	1.57	0.66
								Aver	0	35.5	85.1	1.64	0.65
B I	10	8 3	4.0	318.0	4.3	78.7	1.9	31.5	42.4	3	87.7	1.60	0.63
		7 8	37	413.0	36.0	279.0	1.8	31.8	44.0	5.9	71.4	1.6	0.63
		3 4	50	1300.0	4.0	630.0	7.0	217.0	34.9	3.9	56.4	1.61	0.68
		2	54.1	1447.0	40.0	7 8.0	8.7	2 3.0	11.0	5	50.0	1.57	0.0
		6	4.4	1746.0	38.7	1070.0	6.5	306.0	47.6	3.6	76.0	1.59	0.68
								Aver	40.1	27.4	64.3	1.60	0.68
J H	1.8	1 8	8.0	3 3.0	3.5	1084.0	11.7	110 0	56.6	31.1	9.9	1.03	0.60
		8	54.0	0 3.0	31.0	10 0.0	14.8	1380.0	53.2	35.7	08.9	1.81	0
		1	50.0	2180.0	30.5	10 5.0	15.0	1340.0	51.8	34.3	06.9	1.55	0.66
		1 0	4.0	23 0	30.1	10 5.0	13.3	1120.0	54.8	5	90	1.66	0.6
		1 7	3 0	5 0	29.5	1080.0	11.6	10 0	5 4	31.2	90.7	1.63	0.61
		1 7	4.5	2 8 0	0	10 0	9.7	9 6 0	56.2	34.0	83.3	1.59	0.61
		0	6.0	518.0	33.7	06 2	12.1	187.5	45.2	30.2	76.8	1.69	0.6
		0 4	5 3	460.0	33.0	10	12.8	16 0	42.8	9	69.7	1.63	0.0
		7	1.5	365.0	3 7	2 4	1.7	77.0	44.7	2	73.3	1.66	0.6
		3 8	48.0	1145.0	3 1	4 3.3	1	4 0.0	41.7	31.5	75.1	1.51	0.63
		2 9	43.0	1218.0	31.9	644.1	11.8	635.0	46.1	1	8 9	1.86	0.69
		2 9	3.0	1110.0	31.5	63.5	11.0	60.0	40.3	34.1	87.5	1.45	0.5
								Aver	51.3	3 9	85.7	1.6	0.64
Mean									32.9	36.8	91.4	1 4	0.63

Jolliffe and Chasis[10] have shown in 13 medical students that the creatinine clearance exceeds the xylose clearance by amounts ranging from 25 to 130 per cent, and averaging 74 per cent Since these data may be of value in the interpretation of the widely used creatinine clearance tests, and since they have never been published in detail before, they are presented here *in full in Table 13* *They* show remarkable uniformity in the ratios of the creatinine or urea clearances to the xylose clearance, irrespective of urine volume (*above the augmentation limit*), and illustrate the degree of constancy of each of these clearances that may be expected under controlled conditions

In view of all the above observations, the results obtained on man can be interpreted only as indicating that creatinine is secreted here as in the dog and dogfish In the largest doses of phlorizin administered to man, the creatinine clearance was not significantly depressed[2] In view of the danger attending the intravenous injection of this drug no attempt was made to determine whether larger doses would depress the creatinine clearance or not

COMPARISON WITH UREA CLEARANCE

There is an evident constancy in the ratio of the urea clearance *to the xylose clearance in dogs and in man under various conditions.* With few exceptions the urea-xylose ratio in dogs is above 0 5 and usually runs close to 0 7 at moderate to high urine flows (or low U-P ratios) when the urine flow is *above the augmentation limit* It may be that some urea is reabsorbed by the tubules after the reabsorption of water has been effected and in consequence of a high concentration gradient between the tubular urine and the plasma, as Rehberg[73] has suggested, but this appears to be an inadequate explanation of the fact that the urea clearance remains persistently at a level of about 70 per cent of the xylose or sucrose clearance at all urine flows above the augmentation limit In the absence of direct experimental evidence it is futile, however, to speculate upon possible explanations for this phenomenon

CLINICAL APPLICATIONS OF CLEARANCE OF NON-METABOLIZED SUGARS

The introduction of the urea clearance test (Austin, Stillman and Van Slyke,[1] Moller, McIntosh and Van Slyke[25]) appears to the author to be the most valuable practical contribution made to renal physiology in recent years Although the discrepancy between the urea clearance and these other clearances cannot be explained at this time, he can see no reason for supplanting the urea-clearance *test at this moment in* the usual clinical investigations Apart

from any theoretical uncertainties attached to the use of non metabolized sugars the technical difficulties of determining these substances accurately in plasma and urine offset for the most part any clinical advantage that might be gained from them It should be pointed out therefore that the laboratory of the Department of Physiology of New York University has never recommended the non metabolized sugars for routine diagnostic purposes

Summary —1 In widely separated animals—the dogfish the dog and man—the non metabolized sugars xylose and sucrose are excreted by the kidneys apparently as indifferent substances They have been shown to be completely filtrable from the plasma in simultaneous experiments in normal animals they have identical clearances and in the phlorizinized animal the glucose clearance is brought up to the xylose or sucrose clearance without ever significantly exceeding the latter In the dog xylose sucrose and raffinose are excreted in simultaneous experiments at the same rate of clearance In view of these facts and the further fact that the

that the rate of their excretion relative to the plasma level may be taken as a measure of the rate of glomerular filtration

2 In the dogfish the dog and man the creatinine clearance normally exceeds the xylose or sucrose clearance by a variable but always significant amount In the dogfish this excessive clearance of creatinine amounts to several hundred per cent of the sugar clearance in man 70 to 120 per cent and in the dog 30 to 50 per cent After the administration of phlorizin to the dog the simultaneous creatinine glucose xylose or sucrose clearances become equal and in the dogfish the creatinine clearance is reduced nearly to the level of the other substances As a rule this results from a fall in the creatinine clearance rather than from a rise in the xylose or sucrose clearance The above facts are interpreted to indicate that creatinine is excreted by tubular secretion in addition to glomerular filtration

3 In the dogfish the tubular clearance of creatinine is related to the plasma level of this substance the clearance falling as the plasma level is increased This result is consonant with the supposition that the energy available for the secretion of creatinine is *constant*

4 In the dog the inorganic phosphate clearance is related to the plasma level of this substance in such a manner that as the latter is increased by the injection of phosphate the clearance rises

investigations carried out in this laboratory He wishes to express his appreciation of the assistance of Herbert Chasis, Robert W Clarke, Norman Jolliffe, Robert F Pitts and James A Shannon in the preparation of the manuscript

He also wishes to express his thanks to the editors for their invitation to participate in this volume

ADDENDUM Since this article was prepared, study of the renal excretion of the polysaccharid inulin (mol wt, 972 or greater) has [illegible] tment of [illegible] Westfall [illegible] nnon[29a]) Both groups have found that inulin is not excreted by the aglomerular kidney, and that in normal dogs inulin clearance, at moderate or high rates of urine flow, is approximately the same as that of creatinine, and significantly greater than that of xylose In addition the New York University investigators find a similar dis- [illegible]

if xylose (or sucrose) is reabsorbed either actively or passively, the use of these substances for the measurement of glomerular filtration is, of course, invalidated by so much

REFERENCES

1 AUSTIN, J H, STILLMAN E AND VAN SLYKE D D 1921 Factors governing the excretion rate of urea J Biol Chem, 46 91–112

2 CHASIS H, JOLLIFFE N, AND SMITH, H W 1933 The action of [illegible] creatinine and urea by

[illegible] sorption and excretion [illegible] The use of xylose as a [illegible] Cell Comp Physiol, [illegible]

[illegible]

6 FISHBERG, E H 1930 [illegible] from the blood stream J Biol Chem, 86 665–670

7 GREENWALD I 1931 The possible significance of l xyloketose (urine pentose) in normal metabolism J Biol Chem 91 731 734

8 HOGAN A G 1914 The parenteral utilization of disaccharide sugars J Biol Chem, 18, 485–496

9 JOLLIFE, N 1930 [illegible] erular kidneys, Proc Soc [illegible]

10 JOLLIFFE, N, AND [illegible] exogenous creatinine in man, Am J Physiol, [illegible]

101 [illegible]
13 JOLLIFFE N AND SMITH H W 1931 The excretion of urine in the dog I The urea and creatinine clearance on a mixed diet Am J Physiol 98 572–577
The urea and
–107
33 The renal
n J Physiol

J [illegible] 101 [illegible]
le function of the glom
–10
928 The structure and
l Johns Hopkins Hosp
43 205–235
20 ———— 1932 The function of the proximal convoluted segment of the renal tubule, J Cell Comp Physiol 1 161 176
21 MENDEL L B AND KLEINER I S 1910 The fate of saccharose after

24 ———— 1932 Pentose metabolism II The pentose content of the tissues of the white rat after the oral administration of d xylose J Biol Chem 98 141 150
25 MÖLLER F McINTOSH J F AND VAN SLYKE D D 1928 Studies of urea excretion II Relationship between urine volume and the rate of urea excretion by normal adults J Clin Invest 6 427–465
26 PITTS, R F 1933 The excretion of urine in the dog VII Inorganic phosphate in relation to plasma phosphate level Am J Physiol 106 1–8
26a ———— The clearance of creatinine in the phlorizinized dog Am J Physiol 109 542–549
27 RALLI F P BROWN M AND PARIENTE A 1931 The urea-clearance test in normal dogs Am J Physiol 97 432–438
28 REHBERG P B 1926 Studies on kidney function I The rate of filtration and reabsorption in the human kidney Biochem J 20 447–460
28a RICHARDS A N WESTFALL, B B and BOTT P A 1934 Renal excretion of inulin creatinine and xylose in normal dogs, Proc Soc Exp Biol Med 32 73 75
29 SHANNON J A 1934 Absorption and excretion of water and salts of the elasmobranch fishes IV The secretion of exogenous creatinine by the dogfish Squalus acanthias, J Cell Comp Physiol 4 211 220
29a SHANNON J A 1934 The excretion of inulin by the dogfish J Cell Comp Physiol 5, 301–310
30 SHANNON, J A JOLLIFFE, N AND SMITH H W 1932 The excretion upon the
e filtration

32 Smith, H W 1930 The absorption and excretion of water and salts by marine teleosts, Am J Physiol, 93, 480–505
33 ———— 1931 The absorption and excretion of water and salts by the elasmobranch fishes I Fresh water elasmobranchs, Am J Physio, 98, 279–295
34 ———— 1931 The absorption and excretion of water and salts by the elasmobranch fishes II Marine elasmobranchs, Am J Physiol, 98, 296–310
35 ———— 1931 The regulation of the composition of the blood of teleost and elasmobranch fishes, and the evolution of the vertebrate kidney, Copeia, 4, 147 152
36 ———— 1932 Water regulation and its evolution in the fishes Quart Rev Biol, 7, 1–26
37 White H L and Monaghan B 1933 A comparison of the clearance of various urinary constituents, Am J Physiol, 104, 412–422
38 ———— 1933 A comparison of the clearances of creatinine and of various sugars Am J Physiol, 106, 16–27

CHAPTER VI

THE RÔLE OF THE TUBULES IN THE RENAL EXCRETION OF WATER

By H L WHITE M D

Introduction —The volume of urine may conceivably be varied in three ways by variations in the volume of glomerular fluid by fluctuations in the volume secreted by the tubules and by alterations in the volume reabsorbed by the tubules The various mechanisms by which glomerular output may be varied such as changes in the colloidal osmotic pressure of the plasma in glomerular capillary

at present most workers actively engaged in glomerular physiology are agreed that glomerular function is very probably a passive process Since there is no convincing evidence that the tubules secrete any significant amount of water this possibility will also not be considered This chapter will therefore concern itself with the last of these three factors the role of the reabsorptive function of the tubules in effecting variations in the urinary output of water

DIRECT EVIDENCE OF TUBULAR REABSORPTION

Observations on the Amphibian Kidney —Bieter and Hirschfelder[4] believe that a considerable reabsorption of water occurs in the frog s tubule since a dye color deepens during passage down the tubule They felt that this deepening could not be due to

thus not proved to be due to water reabsorption unless we accept tubular secretion of phenol red as disproved Richards and Walker[16]

find a definite deepening of color in about the middle third of a blocked tubule into which phenol red has been injected *via* the capsule This is obviously due to reabsorption of water

When however the tubule is unobstructed and the passage of dye solution not unduly delayed the evidence for water reabsorption is less striking Hayman and Richards[15] report a precipitate of various intracapsularly injected dyes as they pass down the tubule but apparently did not consistently see any striking deepening of color One might raise the point that the observed precipitation might be due to variations in the salt content of the medium as it passes down the tubule rather than to an abstraction of water but this suggestion is of no great value without more information on both the solubilities of the dyes as affected by salts and on the composition of the tubular fluid In a number of instances Hayman and Richards report that the color produced by glomerular fluid after subcutaneous injection of the dye or chromogen was of about the same intensity as that produced by bladder urine indicating little or no tubular reabsorption of water In the author's experience (unpublished) with both the frog and Necturus a deepening of color as an intracapsularly injected dye solution passes down an unobstructed tubule has been observed at times but is not at all a consistent finding although with the tubule obstructed just below the capsule it is a very striking phenomenon particularly in the frog Bieter[4] finds evidence of water reabsorption by an obstructed tubule which is diminished by HgCl the solutions being introduced *via* the ureter Richards[3] had found that the HgCl-damaged tubule may carry out an even more complete reabsorption of the glomerular product than the normal tubule

fluid moved passively in the cyanide kidney may be as great as that actively reabsorbed in the normal kidney This assumption can at present be neither proved nor disproved because of lack of information on the pressure in the peritubular capillaries although it may be pointed out that earlier in the same paper (pp 86-87) Richards and Barnwell suggested that the pressure within the tubular capillaries was probably high enough to overcome the osmotic pressure of the plasma proteins and force some water out Leaving as unsettled for the present the question of whether tubular capillary pressure or plasma osmotic pressure preponderates (and recognizing that the equilibrium may possibly be shifted in either direction)

the attitude seems reasonable that, while the failure of cyanide to cause marked diuresis in the frog is presumptive evidence that the volume of glomerular fluid does not greatly exceed that of the bladder urine, it is not convincing proof

The strongest argument in favor of a marked reabsorptive capacity by the plasma proteins through a damaged tubular wall is Richards's observation that anuria may exist with normal or increased rate of glomerular filtration The possibility that the tubular lumen may have been obstructed by swollen epithelium does not, however appear to have been excluded, this would not interfere with collection by capsular puncture Richards and Barnwell's observation that dye may be concentrated in the tubules of an excised kidney by tubular reabsorption of water, is again an example of allowing a long time for such a reabsorptive process to operate as is also their observation that phenol red solution which had entered the tubular lumen by glomerular filtration from an arterial perfusate becomes concentrated within seven to fifteen minutes after arterial perfusion is stopped renal portal perfusion with a dye free perfusate being continued Richards and Barnwell feel that the high rates of collection of glomerular fluid which are possible in the frog amount to proof that the total volume greatly exceeds the volume of bladder urine Richards states that There is good reason for believing that more than 90 per cent of the water of the glomerular filtrate is taken from the lumen of the tubule back into the blood The arguments for this stand appear well nigh overwhelming at a rate of 1 c mm of glomerular fluid per hour with 7000 glomeruli in the two kidneys of a 50-gm frog we have 7 cc of glomerular fluid per hour This is certainly more urine than a frog normally puts out, Adolph's average of 1 3 per cent of body weight per hour would give 0 65 cc of bladder urine per hour Richards's calculation leads to a comparable conclusion At the same time it is very probable that the rate of 1 c mm per hour is considerably greater than the average for all glomeruli One naturally selects the most promising capsule for a collection An approximation to an answer to this question could be reached only by subjecting the kidney to some influence which would presumably arouse all of the glomeruli to their maximum activity and collecting from what appears to be an average capsule rather than from one of the best urine from a cannulated ureter would be collected during the same period and the number of glomeruli afterward determined The size of the particular glomerulus used could be determined in the sections to check up on how nearly average it was in that respect

White found that the intracapsular pressure in Necturus, calculated on the assumption that all the glomerular fluid traversed the entire length of the tubule, agreed well with the observed intra-

capsular pressure indicating that the volume of fluid was not greatly changed in passing down the tubule It was realized however, that reabsorption in the lower part of the tubule might not be recognized by this method

To summarize the evidence from microscopic observation of the amphibian kidney it may be stated positively that a considerable proportion of water can be reabsorbed from the tubular lumen if its stay in the tubule is prolonged The evidence is less certain but may be tentatively accepted that a considerable fraction of the *fluid is reabsorbed during a normal passage*

INDIRECT EVIDENCE OF TUBULAR REABSORPTION

Evidence From the Amphibian Kidney —Reports from Hober s laboratory (Scheminzky[38]) show increases of urine volume of from 50 to 100 per cent following narcosis or asphyxia of the frog s tubules Oliver and Shevky[27] found the water output of the winter frog s kidney increased about 250 per cent occasionally more by narcosis or damage of the tubules While they cite no experiments on tubular narcosis with summer frogs the inference is that there *would be little or no increase since they state that with tubular* narcosis the water output of the winter frog rises to the normal for a summer frog Both of these reports are on perfusion experiments with a protein free perfusate and therefore do not conflict with Richards and Barnwell s explanation of the failure of tubular damage to cause diuresis when the kidney is supplied with blood Miyamura[24 25] finds that if the renal portal veins in an intact frog or toad are ligated greatly reducing the tubular circulation the output of water is unchanged in summer frogs or toads well supplied with water increased in dry summer animals and in winter animals the increase being more pronounced with dry than with moist *animals This seems best interpreted by the view that the amphibian tubule may or may not reabsorb water according to the organ*ism s need It follows that while renal portal ligation depresses

th n thel m to lose ts selective

ls

e

r

asphyxial agent and glomeruli with normal blood instead of us ig a protein free perfusate as Scheminzky and Oliver and Shevky have done If there is no increase in water output on tubular narcosis of winter frogs kidneys supplied with blood Richards and Barnwell s explanation must be accepted

So far the author tried merely to answer the question whether or not and to what extent the amphibian tubule reabsorbs water, to him it appears most probable that a significant amount of reab*sorption may or may not occur, depending upon existing conditions*

Until the question of water reabsorption by the "normal" amphibian tubule is definitely answered investigations designed to influence such reabsorption by deliberate changes in salt drug or hormone content of the medium would appear premature A number of such investigations have been carried out only a few can be mentioned Kusakari and Takeda[31] find that adrenalin and atropine decrease the water output of the perfused summer toad's kidney (protein free perfusate) This is in part due to their vasoconstrictor

lium increasing the latter's avidity for and reabsorption of water Pilocarpine has the opposite effect on the tubules over and above its vasodilator action The question of glomerular penetration by renal portal perfusate must always be borne in mind in interpreting such experiments The authors believe they have excluded this, they used perfusing pressures of 24 and 7 cm H_2O for arterial and renal portal perfusions respectively and observed no change in rate of arterial perfusion when adrenalin was added to the renal portal perfusate While this may not be universally accepted as an adequate criterion the increasing recognition of a need for controls on glomerular penetration by renal portal perfusates raises the hope that the existing confusion in this type of work may some day be cleared up

Evidence on Reabsorption by the Mammalian Tubule — Measurements of glomerular filtration Limitation of space as well as dearth of real information precludes a satisfactory discussion of the rôle played by the mammalian tubule in regulating the output of water Since the primary question of the relation between hourly glomerular output and hourly urine volume cannot be answered with certainty one obviously cannot discuss intelligently the effect of drugs hormones etc on this relation Two courses

[illegible] ual and then [illegible] the other is to try to devise procedures which will presumably have little or no effect on the rate of glomerular output and ascribe any observed changes in urinary volume to changes in tubular reabsorption A vast number of reports falling into each of these two general groups is extant The simplicity of the former conception and one's ability upon its basis to calculate the amounts and percentages of reabsorbed solids as well as of water make a strong appeal While its applicability has been obvious since Cushny enunciated the concept of no-threshold substances it remained for Rehberg to apply it to a wide variety of physiological and pathological conditions and to state formally the principle of passive backdiffusion Holten and Reh-

berg[17] find that the hyposthenuria isosthenuria and polyuria of Bright's disease are probably due to diminished tubular reabsorption of water Uremic symptoms disappear quickly when the volume of filtrate is well maintained slowly when it is small and they persist when it is greatly decreased In glomerulonephritis renal arteriolarsclerosis and amyloid disease the volume of filtrate is reduced the amount of reduction depending on the gravity of the case Considerable glomerular damage may exist with but little impairment of tubular reabsorptive power although the latter may also be impaired in true glomerulonephritis Wyschegorodzewa[19] finds that the oliguria of nephrosis is due to increased tubular reabsorption the glomerular filtration rate remaining normal while in nephritis filtration is diminished and reabsorption may be normal The diuresis of diabetes insipidus is due to decreased reabsorption Most of Wyschegorodzewa's work was done contrary to Rehberg's specifications without having raised the plasma creatinine level It is interesting to note that he finds values for filtration rates comparable with those obtained by Rehberg Since as Peters and Van Slyke[28] say about the chromogenic substance spontaneously occurring in the plasma It is uncertain what the substance thus calculated as creatinine is except that it is not creatinine his results are of questionable significance Ni and Rehberg[28] find that the increase in urine volume in the recumbent as compared with the standing posture is accompanied by a decrease in the protein content and colloidal osmotic pressure of the plasma and by an increase in filtration rate There may also be a decrease in tubular reabsorption in recumbency but this is not invariable

The fact that one may not accept the premises upon which this work is based and may choose to substitute tubular secretion of creatinine for Rehberg's rate of glomerular filtration while it detracts from its theoretical significance does not invalidate it as a practical diagnostic and prognostic procedure The probability that this concept actually rests upon a sound theoretical basis is supported by the finding of Poulsson[29] that a close parallelism exists between the concentration ratios of glucose (under phlorhizin) and creatinine although the ratios were not identical Although he did not determine plasma sulphates Poulsson[30] further found that when the urinary concentration of inorganic sulphate is plotted against the concentration ratio of creatinine the points fall reasonably well on a straight line he considered this as evidence that sulphate is concentrated to about the same extent as creatinine The inadequacy of this evidence is shown by the findings of Hayman and Johnston[14] of Cope[10] and of White and Monaghan[47] that the clearance $\left(\frac{\text{urine content}}{\text{plasma content} \times \text{urine volume}}\right)$ of inorganic sulphate is much less than that of creatinine

Jolliffe, Shannon and Smith[19] and Shannon, Jolliffe and Smith[40] report that the clearances of raffinose, of xylose, of sucrose and (under phlorhizin) of glucose are identical and that the clearance of creatinine is, in the dog, 15 to 40 per cent greater than that of the inert sugars. Jolliffe and Chasis[13] report that in man the clearance of creatinine is about 75 per cent greater than that of xylose. Smith and collaborators conclude that the clearance of any of the inert sugars may be taken as the glomerular filtration rate and that the extra creatinine is secreted by the tubules. White and Monaghan[43] failed to find the almost complete identity of clearances of the various inert sugars reported by Jolliffe, Shannon and Smith, but do find that they are rarely more than 40 per cent apart. Creatinine clearance is 25 to 90 per cent higher than xylose and 15 to 50 per cent higher than sucrose. They feel that creatinine or (under phlorhizin) glucose clearances are a better measure of glomerular filtration than xylose or sucrose. Regardless of whether the creatinine or the xylose-sucrose clearance is taken, the glomerular filtrate so calculated is many times the volume of urine, from 10 to 200 times depending on the rate of urine flow. Shannon, Jolliffe and Smith and White and Monaghan, as well as earlier workers, find that the creatinine clearance is not influenced by the plasma creatinine level or by a water diuresis. The clearances of the sugars referred to above are also independent of the plasma levels and water outputs; even if these clearances are not a quantitative measure of filtrate volume, it is at least probable that they are proportional to it.

The other course referred to at the beginning of this section yields results more difficult of interpretation, although certain conclusions can be definitely stated. Thus an intravenous injection of a strongly hypertonic salt solution may increase the urine flow fiftyfold above the resting level. This, to be sure, is probably due in part to an increase in glomerular filtrate, but it is beyond all probability that the volume of filtrate is increased to any such

osmotic resistance to the passage of water from lumen to cell. In other cases, however, as with drinking water, the mechanism is less evident.

Various attempts have been made to distinguish between the glomerular and tubular roles in regulating renal output of water in the mammal, none with complete success. Such procedures as excision of the renal medulla, asphyxia and the use of poisons or narcotics designed to act selectively on the tubules have been employed. Thus Starling and Verney[43] found a considerable increase in urine flow on adding cyanide to the blood of a heart-

lung kidney preparation, this being ascribed to an abolition of tubular function MacNider[43] found a persistent polyuria in the chronic nephritis of uranium nitrate in dogs, the lesions being confined largely to the proximal convoluted tubule There seems to be no question, on the basis of *experiments other than those* purporting to measure glomerular filtration-rate, that mammalian tubules reabsorb a large part of the glomerular filtrate

The Effect of Drinking Water on the Tubular Reabsorption of Water — Many papers on water diuresis have appeared but no quantitative conclusions on the relative roles played by glomeruli and tubules can be drawn unless one accepts the clearance of some substance as creatinine or inert sugar, *as a measure of glomerular filtration* Examinations of the plasma with respect to changes in electrolytes protein and total solid content plasma volume, colloidal osmotic pressure, etc have been carried out but no conclusive explanation of the processes involved has appeared Rioch[37] found that isotonic saline by mouth constantly produced in unanesthetized dogs a low delayed diuresis with a slight increase in serum electrolytes and a *considerable dilution of total solids* With water there were a constant but very variable dilution of total solids and a constant slight dilution of electrolytes The diuretic response always lagged from fifteen to twenty minutes behind the serum changes Smirk[42] found that following either water or isotonic NaCl solution by mouth in unanesthetized rabbits there were usually a dilution of hemoglobin of blood total solids and of plasma total nitrogen and a reduction in percentage cell volume but there was no correlation between the extent of the dilution and the degree of diuresis

Heller and Smirk[16] in a series of papers report a large number of observations among which are that in the guinea pig and rat the tissue load of absorbed but unexcreted water reaches a *maximum* from twenty to forty minutes before the maximum diuresis, but that in the rabbit alimentary absorption is not much in advance of excretion, that the rate of urine flow is not proportional to the existing water load that the diuretic response of rabbits to a given dose of water is less in a warm than in a cool environment but that this is not primarily due to the increased extrarenal water loss [illegible] ...nment and

depend upon an excess of water in the tissues but may [illegible]

pitressin which as has long been known, greatly reduces [illegible] diuretic response to water, that pitressin does not retard the ab-

mentary absorption of water, and, finally, that in rats alimentary absorption of water is delayed and diuresis inhibited by ether and chloroform, but that the inhibition of diuresis persists even when the water absorption is allowed to take place before the anesthesia. A delay in diuresis was confirmed by Klisiecki, Pickford, Rothschild and Verney,[50] who found that the peak of the tissue water load in unanesthetized dogs after 250 cc of water by stomach tube preceded the peak of urine flow by fifteen minutes, the water load had fallen to 75 per cent of maximum by the time the urine flow had reached maximum. Denervation of one or both kidneys does not influence the response. The water diuresis is inhibited by exercise, this is not due to any diminution in absorption from the intestines and it occurs with a denervated kidney as with a normal. Diminished urine flow is accompanied by a rise in urine chloride concentration. The inhibition of diuresis by postpituitary extract is the same with a denervated as with a normal kidney, there is no diminution in intestinal absorption.

All the evidence favors the view that the diuresis from drinking water depends upon a diminished tubular reabsorption rather than an increased glomerular filtration. This view is confirmed by clearance measurements of creatinine and inert sugars. What the

if the injection is made at such a rate as not to produce much hemolysis. The view that increase in water content in plasma acts directly on the kidney cells fails, as Verney and collaborators[50a] point out, to explain other very similar polyurias, *i e*, those of diabetes insipidus, hypophysectomy, piqûre and of the isolated mammalian kidney, in none of which is there an increase in water content of plasma but rather a decrease. There is with the above-mentioned polyurias a deficit of postpituitary secretion and the polyuria is abolished by the secretion. Verney believes that water diuresis is brought about by a diminution or abolition of the secretion by the posterior pituitary of a hormone which maintains the normal capacity of the tubular cells to reabsorb water. When the

mediation of the nervous system, by the concentration of water in blood and tissues, being diminished by an excess of water. The lag in the diuretic response behind the water load is assumed to be due to the time required for the disappearance of the preexisting

antidiuretic h by exercise
must on this secretion
To quote Ve ere to the
pituitary hyp itration of
water in the blood to be the mediate stimulus to the kidney in water excretion those who adhere to the hypothesis of Haldane and Priestley (1916) believe it to be the immediate stimulus This concept is considerably weakened by the recent finding of Newton and Smirk [58] that totally hypophysectomized decerebrate cats show the same lag of diuresis behind water load as do normals Similar experiments on diabetes insipidus patients might be worth while

Fremont Smith and collaborators [2] found no significant serum dilution or change in creatinine clearance during the diuresis of water-drinking in normal human subjects In edematous or febrile subjects or after pituitrin injection the diuresis was abolished or delayed and serum dilution occurred They explain the diuresis without increase in creatinine clearance (considered a measure of glomerular filtrate) by the assumption that in this diuresis the total

correspondingly shorter time available for tubular reabsorption There is thus a smaller percentage tubular reabsorption not because of an actual lessening of the reabsorptive function of the tubules but merely because the opportunity for reabsorption is diminished Recognizing that any statement on this topic must be one of opinion rather than of demonstrated fact it seems to the author more

time for the reabsorptive process to be carried out

The Effect of Salts and Acids on the Renal Output of Water —An adequate discussion of this topic will not be attempted since we are trying to confine ourselves to the tubules A large amount of information exists on the kidney s response to varying intakes of water salts and acids and the changes in water output are very probably due primarily to changes in the extent of tubular reabsorption but an unqualified differentiation between the glomerular and tubular roles cannot be made The papers of Adolph [12] White [45] and Hansen Fosdick and Dragstedt [13] may be cited Chabanier Lobo Onell and Lélu [9] followed plasma Na and Cl and urine Na Cl and pH before during and after the administration of water isotonic and hypertonic NaCl solutions insulin and a mercurial diuretic neptal Their findings which are not new, are (1) That an increased water output shifts the urine toward alkalinity and *vice versa* (2) that the pH of the tubular epithelium changes in the

direction opposite to that of the urine anions being attracted to the epithelial cells when cations are in excess in urine, and *vice versa* Differences in the plasma salt content on water, salt and neptal diuresis are discussed but the details cannot be considered here, suffice it to say that the results cannot be explained on the basis of these changes without postulating a variability of the tubular cells reaction to their environment The increased basicity of the urine on diuresis is explained as due to a shift in the isoelectric point perhaps hormonally produced of the tubule cells This would mean according to the reabsorption view that on diuresis the isoelectric point shifts toward the alkaline side the protoplasm

r anions The

tubular secre-

the facts An

increased avidity of the cells for cations would explain the latter s removal from the blood stream but the process must be reversible to permit their liberation into the tubular lumen The required postulates become very complex as one tries to explain the differences in the salt outputs of water salt and neptal diuresis two sets of cellular proteins being required whose isoelectric points shift reversibly in opposite directions Fantastic as these considerations may seem it has long been obvious to workers interested primarily in the mechanisms rather than the end results of cellular activities that some such process or processes must be operative although the mechanism is obscure This type of conception assigns to the tubules the major role in effecting fluctuations of urinary water output Keller[20] believes that to a large extent the tubular reabsorption of water and other constituents is explained by their electrical charges with respect to those of the cells Among other examples are the reabsorption of positively charged water by the negatively charged protoplasm of the proximal tubule cells, acid diminishes the negative charge of the cell constituents concerned thereby diminishing the reabsorption of water The reabsorption of the negatively charged glucose is assigned to certain cell constituents shown by staining reactions to be positively charged He cites Gicklhorn s demonstration that the zone of tubule stained by acid (negative) dyestuffs is increased by decreasing the pH of the environment

Further Consideration of Drugs and Hormones —Bieter[5] finds that

of the urine so obtained is the same as that of the caffeine urine indicating that the effect was primarily glomerular However some of the work on creatinine clearance, mentioned below, favors the view than xanthin derivatives also influence tubular reabsorption of water Richards and Schmidt showed that small doses of pituitrin may increase glomerular circulation while large doses may decrease it If however, clearance of creatinine or of inert sugar is considered as a measure of or proportional to the glomerular filtrate the findings of Poulsson[30] and of Burgess, Harvey and Marshall[7] *indicate no change in glomerular filtration during the* antidiuretic action of pituitrin in the mammal The latter workers *found further that pituitary extract is antidiuretic in the bird and* reptile but not in the amphibian or fish that the antidiuretic action in the bird is sometimes but not necessarily accompanied by a *decrease in glomerular filtration as measured by inert sugar clear* ance and that in the reptile the glomerular filtrate is very greatly reduced by pituitrin The antidiuretic effect in the mammal or bird is ascribed to an increased water *reabsorption by the thin* segment of the loop of Henle The fish and amphibian have no loop and do not exhibit the antidiuretic response The reptile also lacks a loop of Henle but the antidiuretic response is apparently due to a great reduction in glomerular filtration which effect is not [illegible] the bird It seems most [illegible] trin in normal mammals [illegible] in diabetes insipidus is best explained by assigning to the hormone the ability to increase the tubular reabsorption of water

Verney and collaborators[20a] find that thyroxin subcutaneously opposes pituitrin *i e* it increases the intensity and shortens the duration of water diuresis Silvette and Britton[41] showed that adrenalectomized rats give a lower diuretic response to intra peritoneally injected water or aqueous solutions than do normal rats The response of adrenalectomized rats was restored to normal on the administration of adrenal cortex extract *but the extract did not* influence the response of normal rats The water content of the tissues of adrenalectomized rats is greater than normal, in adrenal *ectomized cats the water content of certain tissues as liver and* skeletal muscle is increased that of the blood and kidneys is decreased and that of the skin spleen and brain unchanged It is concluded that the diminished ability of adrenalectomized animals

[illegible] nine clearance [illegible] urial diuretics, according to their findings [illegible] gated produce tubular diuresis Schmitz[39] finds no change in creatinine clearance with an organic mercurial (salyrgan) diuresis but finds an increase

on a xanthin (euphyllin) diuresis he also found an increased
creatinine clearance on the diuresis of intravenous injections of
isotonic NaCl solution However Liggett and Grant[7] found no
change in creatinine clearance in the diuresis produced by sn n
doses of NaF intravenously If this clearance is considered a
quantitative measure of or even proportional to the rate of gl
erular filtration it is thus seen that there is a disagreement not
of interpretation but in the experimental findings on whether
diureses discussed in this section are primarily glomerular or tub
The matter must be regarded as still unsettled It is quite po
that in some cases as with xanthin derivatives there is bo
increase in glomerular filtration and a decrease in tubular rea
tion, the author's personal belief is that the latter is the
important

REFERENCES

1 Adolph E F 1923 The excretion of water by the kidneys Am J
Physiol 65 419 449
2 — 1925 The chemical sensitiveness of the kidneys, Am J
Physiol 74 93 110
3 — 1927 The excretion of water by the kidneys of frogs, Am
J Physiol 81 315 324
4 Bieter R N 1930 The real sorptive function of the tubule in the
frogs kidney Am J Physiol 93 574 587
5 — 1931 The action of some diuretics upon the aglomerular
kidney J Pharm and Exp Therap 43 399–408
6 Bieter, R N and Hirschfelder, A D 1924 The excretion of
dyes and other substances in the frogs kidney and its bearing upon the theories
of renal secretion Am J Physiol 68 326–337
7 Burgess W W Harvey A M and Marshall E K Jr 1933
The site of the antidiuretic action of pituitary extract J Pharm and Exp
Therap 49 237 249
8 Chrometzka F and Unger K 1931 Untersuchungen über die
Grösse des Glomerulusfiltrats unter dem Einfluss von Diureticis und Hormonen,
Ztschr f d ges exp Med 80 201 257
9 Chabanier H Lobo-Onell C and Lélu 1930 Études sur les
diurèses aqueuses et salines J phys et path gen 28 841 853
10 Cope, C L 1932 Inorganic sulphate excretion by the human kidney,
J Physiol 76 329 338
11 Edwards J G and Marshall, E K Jr 1924 Microscopic observa
tions of the living kidney after the injection of phenolsulphonphthalein Am
J Physiol 70 183 415
12 Fremont-Smith F Fremont-Smith M Dailey M E Solomon P,
Stetten DeW Jr and Carroll M P 1930 Studies in edema I The
mechanism of water diuresis in man J Clin Invest 9 7 8
13 Hansen H I Losdick I S and Drabstedt C A 1931 A study
of the effect of certain diuretics on the concentration of blood chlorides in
dogs J Pharm and Exp Therap 41 325 331
14 Hayman J M Jr and Johnston S M 1932 The excretion of inor
ganic sulphates J Clin Invest 11 607 619
15 Hayman J M Jr and Richards A N 1926 Deposition of dyes,
iron and urea in the cells of a renal tubule after their injection into its lumen
glomerular elimination of the same substances Am J Physiol 79 149–16
16 Heller H and Smirk F H 1932 Tissue hydration and diuresis,
J Physiol 76 1 [illegible] and 283 [illegible]
17 Hertzen C and Rehberg P B 1931 Studies on the pathological
function of the kidneys in renal disease especially Bright's disease Acta med
Scand 74 473-518 and 538 565

18 Jolliffe, N, and Chasis, H 1933 Filtration and secretion of exo-

20 Keller, R 1932 Die Elektrizitat in der Zelle, Julius Kittls Nachf
20a Klisiecki, A, Pickford, M, Rothschild, P, and Verney, E B 1933 The absorption and excretion of water by the mammal, Proc Roy Soc, B, 112, 496–521, and 521–547
21 Kusakari, H, and Takeda, K 1930 Einfluss der vegetativen

25 ——— 1927 The reabsorption of water in the tubules of the Japanese toad s kidney, Japan J Med Sci, IV, Pharmacol, 1, 291–310
25a Newton, W H, and Smirk, F H 1934 The pituitary gland in relation to polyuria and water diuresis, J Physiol, 81, 172–182
26 Ni, T, and Rehberg, P B 1931 On the influence of posture on kidney function, J Physiol, 71, 331–339
27 Oliver J, and Shevky, E 1929 A mechanism of conservation in

itative clinical
604
elimination in

30 ——— 1930 Ueber die Wirkung des Pituitrins auf die Wasserausscheidung durch die Niere, Ztschr f d ges exp Med, 71, 577–720
31 Rehberg, P B 1926 The rate of filtration and reabsorption in the human kidney, Biochem J, 20, 447–460

glomerular circulation in the frog s kidney and observations concerning the action of adrenalin and various other substances upon it, Am J Physiol, 71, 178–208
36 Richards, A N, and Walker, A M 1930 Quantitative studies of the glomerular elimination of phenol red and indigo-carmine in frogs, J Biol Chem, 87, 479–498
37 Rioch, D McK 1930 Water diuresis, Jour Physiol, 70, 45–52
38 Scheminzky, F 1929 Die Farbstoffsekretion der 2 Abschnitte,

104, 399–411

45 WHITE H L 1927 The effect on the urinary output of water chloride [illegible] nd acid content [illegible]

[illegible] n by the renal [illegible] J Physiol 88 [illegible]

47 WHITE H L AND MONAGHAN B 1933 A comparison of the clearances of various urinary constituents, Am J Physiol 104 412–422

48 ——— 1933 A comparison of the clearances of creatinine and of various sugars Am J Physiol 106 16–27

49 WYSCHEGORODZEWA V D 1931 Bestimmung der Nierenfunktion auf Grund der modernen Filtrations-Reabsorptionstheorie der Harnabsonderung Ztschr f d ges exp Med 75 72 82

CHAPTER VII

THE EFFECT OF THE SPLANCHNICS UPON GLOMERULAR BLOOD FLOW *

By RAYMOND N BIETER M D PH D

Introduction —Claude Bernard in 1859 published his findings on the nerve supply of the kidney He was a contemporary of the early triumvirate of kidney physiologists Bowman Ludwig and Isaacs whose publications in 1842 1844 and 1857 respectively ushered in the modern era of kidney physiology

Bernard sectioned the splanchnics in dogs and rabbits and noted that the secretion of urine was increased When the peripheral ends of these nerves were stimulated the secretion of urine stopped and was not resumed during the period of excitation Section of the vagus and stimulation of its peripheral end produced no change in the flow of urine On the stimulation of the central end of the cut vagus he obtained a decrease in the urine output He also observed that section of the spinal cord stopped the secretion of urine but if artificial respiration was administered the urine flow began again In a curarized animal first without respiratory movements and then with artificial respiration he obtained similar results

Bernard from his experiments was greatly impressed with the regulatory role upon kidney activity exercised by the renal nerves by means of their control of the capillary circulation It is interesting in the light of modern work that Bernard conceived the idea of functional intermittency

From Bernard down to the present section of the splanchnics has repeatedly been observed to increase the flow of urine To the results obtained by splanchnic section might be added the findings of investigators who have reported increased urine output from transplanted kidneys principally in the case of autogenous transplants the diuresis lasting at least some days following the operative procedure Here the results have to do with kidneys deprived of their entire nerve supply These investigators are of the opinion that life is compatible with complete denervation of the kidneys and cite experiments of animals living a normal life with a single denervated kidney for as long as six years (*Zaaijer*[24])

* Abstract of Bieter R N 1930 The effects of the splanchnics upon glomerular blood flow in the frog's kidney Am J Phys 91 436–458

Cohnheim and Roy[4] were the first to study the effect of the splanchnic nerve upon kidney volume and blood flow with a technique capable of rendering satisfactory results. They were the first to use the oncometer to study changes in kidney volume. From a series of varied experiments including the section of the splanchnics they were able to show that contrary to their expectation section of the splanchnics did not produce a definite increase in kidney volume, while stimulation of the peripheral ends caused marked contraction as well as rise in blood pressure. Similar reflex contraction was obtained by central stimulation of cut nerves like the sciatic and vagus. In contradistinction to these results experiments upon the completely denervated kidney showed this to increase in size with rise of blood pressure and decrease with fall of pressure. Bradford[5] demonstrated vasoconstriction within the kidney and resulting shrinkage and vasodilatation with expansion of the kidney. From rapid electric stimulation of the posterior roots of the spinal cord Bradford obtained marked constriction of the kidney. He obtained this effect with roots beginning with the sixth dorsal and terminating in the second lumbar, the most marked effect being obtained from stimulation of the roots from the tenth to the thirteenth dorsals. Using a similar stimulus but with a different rate of one or two stimulations per second only on the same cut roots he obtained dilatation of the kidney. Applying these different rates of stimulation to the splanchnic nerves he obtained the same results. Applying them to the peripheral end of the divided vagus Bradford, like Cohnheim and Roy, obtained no effect on the kidney. Stimulating the central ends of divided sensory nerves such as the sciatic, vagus and intercostal he confirmed Cohnheim and Roy in finding reflex contraction of the kidney. Thus it was proven that as far as bloodvessel effects are concerned the kidney is an organ well supplied with vasoconstrictors and, to a lesser extent, with vasodilators.

Another important contribution was added when it was shown by Burton-Opitz and Lucas[7] that section of the splanchnics increases the blood flow through the kidneys, whereas stimulation of the splanchnics decreases the flow. Later Burton-Opitz showed that the right and left splanchnics were distributed to the right and left kidneys respectively.

Thus section of the splanchnics, which removes their influence, results in an increase in urine output, whereas stimulation of their peripheral ends, which leads to an increase in their function, results in a decrease in urine output. We associate with this the findings that section of the splanchnics increases the blood flow through the kidney, whereas peripheral stimulation decreases the renal blood flow. Modern kidney physiology now raises the question: What part is played by the glomerulus in these variations of function?

CHAPTER VII

THE EFFECT OF THE SPLANCHNICS UPON GLOMERULAR BLOOD FLOW *

By RAYMOND N BIETER M D Ph D

Introduction —Claude Bernard in 1859 published his findings on the nerve supply of the kidney He was a contemporary of the early triumvirate of kidney physiologists Bowman Ludwig and Isaacs whose publications in 1842 1844 and 1857 respectively ushered in the modern era of kidney physiology

Bernard sectioned the splanchnics in dogs and rabbits and noted that the secretion of urine was increased When the peripheral ends of these nerves were stimulated the secretion of urine stopped and was not resumed during the period of excitation Section of the vagus and stimulation of its peripheral end produced no change in the flow of urine On the stimulation of the central end of the cut vagus he obtained a decrease in the urine output He also observed that section of the spinal cord stopped the secretion of urine but if artificial respiration was administered the urine flow began again In a curarized animal first without respiratory movements and then with artificial respiration he obtained similar results

Bernard from his experiments was greatly impressed with the regulatory rôle upon kidney activity exercised by the renal nerves by means of their control of the capillary circulation It is interesting in the light of modern work that Bernard conceived the idea of functional intermittency

From Bernard down to the present section of the splanchnics has repeatedly been observed to increase the flow of urine To the results obtained by splanchnic section might be added the findings of investigators who have reported increased urine output from transplanted kidneys principally in the case of autogenous transplants the diuresis lasting at least some days following the operative procedure Here the results have to do with kidneys deprived of their entire nerve supply These investigators are of the opinion that life is compatible with complete denervation of the kidneys and cite experiments of animals living a normal life with a single denervated kidney for as long as six years (Zaaijer[24])

* Abstract of Bieter R N 1930 The effects of the splanchnics upon glomerular blood flow in the frog s kidney Am J Phys 91 436–458

Cohnheim and Roy[9] were the first to study the effect of the splanchnic nerve upon kidney volume and blood flow with a technique capable of rendering satisfactory results They were the first to use the oncometer to study changes in kidney volume From a series of varied experiments including the section of the splanchnics they were able to show that contrary to their expectation section of the splanchnics did not produce a definite increase in kidney volume while stimulation of the peripheral ends caused marked contraction as well as rise in blood pressure Similar reflex contraction was obtained by central stimulation of cut nerves like the sciatic and vagus In contradistinction to these results experiments upon the completely denervated kidney showed this to increase in size with rise of blood pressure and decrease with fall of pressure Bradford[8] demonstrated vasoconstriction within the kidney and resulting shrinkage and vasodilatation with expansion of the kidney From rapid electric stimulation of the posterior roots of the spinal cord Bradford obtained marked constriction of the kidney He obtained this effect with roots beginning with the sixth dorsal and terminating in the second lumbar the most marked effect being obtained from stimulation of the roots from the tenth to the thirteenth dorsals Using a similar stimulus but with a different rate of one or two stimulations per second only on the same cut roots he obtained dilatation of the kidney Applying these different rates of stimulation to the splanchnic nerves he obtained the same results Applying them to the peripheral end of the divided vagus Bradford like Cohnheim and Roy obtained no effect on the kidney Stimulating the central ends of divided sensory nerves such as the sciatic vagus and intercostal he confirmed Cohnheim and Roy in finding reflex contraction of the kidney Thus it was proven that as far as bloodvessel effects are concerned the kidney is an organ well supplied with vasoconstrictors and to a lesser extent with vasodilators

Another important contribution was added when it was shown by Burton Opitz and Lucas[7] that section of the splanchnics increases the blood flow through the kidneys whereas stimulation of the splanchnics decreases the flow Later Burton-Opitz showed that the right and left splanchnics were distributed to the right and left kidneys respectively

Thus section of the splanchnics which removes their influence results in an increase in urine output whereas stimulation of their peripheral ends which leads to an increase in their function results

part is played by the glomerulus in these variations of function?

Richards and Schmidt [21] and Richards [9] observed that *stimulation* of the sympathetic fibers to the kidney and stimulation of the central ends of a cut sensory nerve such as the sciatic increased the inter mittency of blood flow through the glomeruli They stated that intermittency of glomerular flow was to be seen even when the brain and spinal cord were destroyed Among influences which may produce vasodilatation and vasoconstriction in the kidney *they counted among the former* section of the sympathetic nerve supply to the kidney and among the latter afferent nerve stimula tion and direct stimulation *of the sympathetic nerve supply to* the kidney They did not present the experimental basis for their pronouncement

MICROSCOPIC STUDIES OF GLOMERULAR BLOOD FLOW

The author has studied the effect of electrical stimulation of the sympathetic nerves to the kidney contained in the splanchnics as *well as the effect of stimulation of the central ends of cut sensory* nerves such as the sciatic and vagus upon the glomerular blood flow in large and small fields of the kidneys of Rana pipiens and Rana catesbiana

Electrical Stimulation of Splanchnic Sympathetic Nerves -- When a frog was prepared as reported in detail elsewhere the kidney brought into focus with the low power of a microscope and the splanchnic of the same side was stimulated it could be seen as Richards and Schmidt[21] have reported that the bloo l flow

the more marked was the effect observed All of the glomeruli did not remain inactive throughout the period of stimulation some resumed flow and in others the flow stopped so that the total number of active and inactive glomeruli showed about the same *relationship during the stimulation* Stimulation of both the upper and lower splanchnic trunks was employed When attention was focused upon one small field (10 experiments) the percentage of arre t was far greater thus in 6 out of 10 recorded experiments on different frogs all of the visible active glomeruli stopped When the stimulus was discontinued the inactive glomeruli resumed flow within two minutes In the case of some glomeruli it has been observed *that only after four or five repeated short* periods of stimulation with a rest period between each has it been possible to stop blood flow Other glomeruli have been stopped two four six eight and ten times by so many successive stimulations with out any apparent difference in their response and return to normal

It has also been noticed during splanchnic stimulation that some fields of kidney tissue become paler than normal appearing as if there is a great vasoconstriction throughout the kidney

The glomeruli that stop as a result of stimulation generally show

where the afferent vessel was visible, this showed a stoppage of flow during the period of stimulation and a gradual emptying of cells into the glomerulus, after which the afferent artery could no longer be seen This would indicate a point of great constriction away from the glomerulus, probably at the point of its origin, as has been shown by Krogh [14] When the electrical stimulation was discontinued, the afferent artery would suddenly show a burst of flow, following which the entire glomerulus would burst into activity, or in other cases the capillaries would assume their flow, one by one, over a period of five to ten seconds

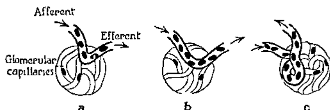


FIG 13 —Diagram of glomeruli from the frog's kidney showing the "shunt" between afferent and efferent glomerular arterioles *Afferent* Afferent glomerular arteriole *Efferent* Efferent glomerular arteriole (Beter Am J Physiol)

glomerular capillary flow, one and occasionally two capillaries remained which, with the afferent and efferent arteries, showed a very rapid flow When this was observed it was found practically impossible to stop the flow with electrical stimulation In every kidney studied in this portion of the work one or two and as high

served that the afferent and efferent arterioles in some cases were

injected whereas the glomerular capillaries remained free of the dye They concluded that a direct loop between these two arterioles within

No attempt has been made to look for them in Rana pipiens

Stimulation of Sensory Nerves —Stimulation of the central ends of cut sensory nerves such as the sciatic and vagus produce the same effects (6 experiments) In each type of stimulation the *number of active glomeruli* was cut roughly in half One animal showed almost an 80 per cent decrease in the number of active glomeruli—a greater decrease than was obtained in splanchnic *stimulation*

eruli tend to

minutes after

flow was fairly close to the previous level In small fields of active glomeruli where the effect of stimulation could be observed con

lar to those obtained with

the splanchnics leads to decreased glomerular flow one naturally wonders what section of the splanchnics will produce This has been determined upon a series of Rana pipiens and Rana catesbiana In every kidney studied (13 experiments) and especially in those kidneys

same side Out of 13 experiments in 8 this has been controlled by counts of the glomeruli in the opposite or normal kidney During the time of the experiment which has run from one to two hours no marked change in these results have been observed Intermittency of glomerular blood flow in these experiments has been the exception rather than the rule The number of active glomeruli after splanchnic section has remained extremely constant up to one and a half hours following the section Occasionally 1 glomerulus out of 70 to 100 may show arrest of flow but when this has occurred the periods of intermittency generally have been long (five to ten minutes) In many cases the glomeruli which showed arrest of flow were apt to continue this way throughout the time of the experiment

In 2 frogs (Rana catesbiana) where observations were carried on for over three hours several small fields in a kidney in each animal were found where the glomeruli showed intermittency of blood flow after splanchnic section During the periods of arrest the afferent arterioles also showed arrest of flow and a complete emptying of red cells into the glomerular capillaries

Most observers have found that kidneys with sectioned splanchnics at first put out urine in amounts increased over the normal but that eventually the urine volume tends to return to normal If the observations reported here that at some time after splanchnic section the glomeruli tend to show some intermittency of flow, are correct these two types of observations may be correlated The immediate effects of splanchnic section are to increase the number of active glomeruli and to increase the volume of urine secreted but sooner or later the afferent arteries and glomeruli establish their own intermittency without nerve control and then the urine volume tends to approximate the original normal level

Clamping the Ureters —Reflex anuria is a condition met with both experimentally and clinically This condition generally arises from some point of excessive stimulation It has been reported by Loucks and Scott[16] from pulling on the kidney stretching muscles and incising the skin in dogs It has been reported by clinicians from inserting a ureteral catheter into the ureter and from instilling drugs such as silver nitrate into the ureter and its association with kidney stones and ureteral kinks is well known Blum[5] reported a case of complete anuria resulting from a surgical procedure in which the ureter was probably caught in a ligature Because of its importance and because of what we know of the control of the splanchnics on kidney blood flow and urine output it was thought worth while to try the effect of some of the procedures known to produce anuria upon the activity of the glomeruli both with normal innervation and without splanchnic innervation

Attention should be called to the fact that immediately after a

following work this is probably the result of reflex closure of the afferent glomerular arterioles

The effect of placing a small bulldog clamp on the ureter was first tried In every one of 8 experiments the number of active glomeruli dropped giving an average decrease for all of the experiments of about 40 per cent The clamp was removed immediately after the count following which the number of active glomeruli began to increase During the next ten to fifteen minutes the glomeruli reached normal levels

When the splanchnic nerves were cut this decrease in active glomeruli was not observed In 5 experiments the number of active glomeruli showed no change neither was there any appreciable change in rate of flow or size of glomeruli Quinby[18] observed that in handling the ureters of denervated kidneys the temporary inhibition of urine flow seen in normal kidneys after handling the ureter did not occur

bichloride applied to the ureter externally produce the characteristic arrest of *glomerular flow* *Again this decrease of glomerular flow* is absent when the splanchnics are cut

Release of Edema Fluid Previously Developed by Ligature of Limb —Andrews[1] while investigating experimental uremia, noticed that when dogs legs developed an edema from too tight a ligature, if then the ligature was removed and the leg massaged anuria occurred Because of this finding rubber binders were placed on the legs of a series of frogs and in twelve to fifteen hours a marked edema was produced The leg below the ligature was from one-half to again as large as the normal leg The frog was now prepared for microscopic observation and as soon as the normal counts of *glomeruli had been obtained the ligature was removed and the* leg massaged gently In all animals 5 in number this resulted in a marked decrease of active glomeruli and the return to normal was not complete for fifteen to twenty minutes Here again the effect was removed by section of the splanchnics as shown in another series of 6 animals with unilateral severing of splanchnic innervation In the normal kidney the active glomeruli were cut down by almost 50 per cent whereas in the kidney without splanchnic innervation no effect upon the number of active glomeruli was produced Some slowing of the rate of flow was noticed in 2 of the denervated kidneys It was thought that this might *have been due to a lowering of blood-pressure but direct determina*tions showed that there was no marked lowering of blood-pressure yet this slowing of blood flow was apparent for at least five minutes The results of the edema experiments on glomerular blood flow again indicate that the splanchnics play a major rôle in their arrest Massaging of normal legs had no definite effect on the number of active glomeruli

Effects of Irritants Injected Into the Ureter and Tubules — Lastly the reflex effects on glomerular blood flow from irritants such as bichloride of mercury solution injected into the ureter and into the tubules was determined

Briefly these experiments showed that 1 per cent bichloride of mercury solutions injected into the ureter and collecting ducts produce a decrease of glomerular blood flow of the same order of magnitude as was observed in other positive experiments described above *This retardation was no more marked* when, by higher injection pressure (25 cm H_2O the mercury solutions were forced up into the convoluted tubules When the splanchnics were previously sectioned no retardation was observed

These experiments gain support from the *anatomical work of*

Smirnow [23] Studying the kidneys of mammals, including man and frogs this investigator found nerve fibers between the epithelial cells of the tubules collecting duct and ureter The endings in the tubules because of their similarity to nerve endings in secreting glands he concluded to be secretory whereas those ending in the collecting ducts pelvis and ureter being more simple in structure than the above he concluded to be sensory In the experiments

The findings here reported upon the function of the splanchnics when stimulated directly or reflexly to decrease glomerular blood flow and in all probability glomerular filtration and the inhibition of this function by local anesthetization of the part stimulated to produce this reflex such as the ureter and by section of the splanchnics are thought to have a clinical bearing Whereas these results were obtained in the frog it is likely that in the frog the vasomotor control of the kidney vessels is not as highly developed as it is in mammals and man and consequently ascending the scale the effects would possibly be more powerful Insofar as they are thus able these results are thought to add confirmations (1) To the the report of Neuwirt [17] who with procaine anesthesia of the splanchnics in a case of kidney stone colic relieved the pain and produced a resumption of urine secretion (2) to the reports of Hess [11 12] who performed renal sympathectomy in 5 cases the result of which was an increased output of urine from the operated kidney and (3) To the report of Rowntree [22] who has studied renal sympathectomy in dogs with similar findings preparatory to applying the procedure clinically

Conclusions —Intermittency of glomerular blood flow and intermittency of capillary flow within the glomerulus in the normal frog s kidney as first reported by Richards [19] is again confirmed Immediately after splanchnic section in the frog this intermittency for the most part disappears At three hours after splanchnic section in 2 cases this intermittency was again to be seen in several small fields of glomeruli but the rest periods were no longer than thirty seconds Section of the splanchnics as an acute effect, results in an increase of glomeruli showing active blood flow

Various measures such as pinching the ureter and applying an irritant locally both externally and internally and edema fluid let into the general circulation result in reflex arrest of glomerular flow This reflex arrest of glomerular flow is prevented by splanchnic section and by cocainization of the part stimulated The reflex

arrest produced by mercuric chloride in the ureter and collecting ducts appears more pronounced than the reflex arrest coming from within the kidney tubules

These experiments show the marked effect of the splanchnics upon glomerular blood flow and as far as they are able tend to explain how local anesthesia and section of renal nerves will produce beneficial results clinically in reflex oliguria and anuria

References

1 Andrews E 1927 Experimental uremia Arch Int Med 40 548-570

2 Bernard C 1859 Leçons sur les propriétés physiologiques et les

1203-1210

6 Bradford J R 1889 The innervation of the renal bloodvessels J Physiol 10 358-407

des rechten Nervus splanchnicus auf die Blutfulle des linken Organs Arch 125 221 229

9 Cohnheim J and Roy C S 1883 Untersuchungen über die Circula

14 Krogh A 1922 The anatomy and physiology of the capillaries Yale Univ Press New Haven

15 Loucks M and Scott F H 1928 Personal Communication

16 Ludwig C 1844 Wagners Handworterbuch der Physiol 2 637

17 Neuwirt K 1923 Ein Beitrag zur Therapie der Reflexanurie Ztschr f Urol Chir 11 75-85

18 Quinby W C 1916 The function of the kidney when deprived of its nerves Jour Exp Med 23 535-548

19 Richards A ... Med Sci 163 1 19

... 284

...ription of the

...ncerning the

... Physiol 71

22 Rowntree L G 1928 Personal Communication

23 Von Smirnow A E 1901 Ueber die Nervenendigungen in den Nieren der Saugetiere Anat Anzeiger 19 347-359

24 Zaaijer, J H 1914 Dauerresultat einer autoplastischen Nieren transplantation bei einen Hunde Beitr z klin Chir 93 223-227

CHAPTER VIII

THE EFFECTS OF DIETARY DEFICIENCY ON RENAL GROWTH AND STRUCTURE

By C M JACKSON M D LL D

The lack of sufficient food or of any one or more of the necessary nutritional factors results in a condition of inanition The various types of inanition are indicated in the following outline

- Inanition
  - A Total (quantitative)
    - 1 Complete (no food whatever)
    - 2 Incomplete (insufficient nutriment general underfeeding)
  - B Partial (qualitative)
    - 1 Complete (entire absence)
    - 2 Incomplete (insufficient amount)
    - of one or more of the necessary foodstuffs
      - proteins
      - fats
      - carbohydrates
      - salts
      - vitamins
      - water

The kidneys, among other organs are somewhat variably affected according to the type of inanition Under each type of deficiency, the effects have been studied in man and lower animals, both young and adult These effects may include changes in renal weight and structure gross and microscopic Some data are also available concerning the renal weight when normal diet is restored

TOTAL (QUANTITATIVE) INANITION

Effects of Total Inanition.—So far as known, the effects on the kidneys are similar during total inanition (with no food or water) and when water only is given so both conditions will be reviewed together. During total inanition renal function and urinary secretion decrease rapidly to a very low level which is somewhat higher in case water intake is permitted The effects of inanition upon the amount and composition of the urine are reviewed by Morgulis (1923), and will here be given only incidental notice

Changes in Weight of the Kidney —Cases of simple starvation are rare in man The best available data are from necropsies during famine or infantile malnutrition although there are frequently complications, especially infections which may affect the kidney It is, therefore, not surprising to find the kidneys from such cases quite variable in weight Table 14 shows the average changes in

TABLE 14 —WEIGHT CHANGES IN ORGANS OF ATROPHIC INFANTS (JACKSON 1925)

Average percentage d fferences [illegible]

Organ				
Brain	+25 9	+1 5	−7 7	−12 3
Lungs*	+24 5	−4 5	−20 6	−21 2
Kidneys	+20 5	−5 7	−1 0	−19 4
Spleen	+9 5	−14 9	−20 5	−31 3
Heart	−0 9	−20 9	−14 9	−28 0
Whole body	0 0	−20 9	−31 6	−51 5
Liver	−6 3	−33 0	−23 2	−27 1
Suprarenals	−43 3	−60 5	−56 9	−38 5
Thymus	−71 8	−80 7	−80 6	−82 6

* Pneumonia cases excluded

relative weight of the kidneys and some other organs from marasmic infants, calculated by comparison with the (estimated) normal weight on various bases In this series of 30 to 50 cases, the final body weight averaged 20 9 per cent below the maximum weight recorded during life, 31 6 per cent below the normal for body *length and 51 5 per cent below the normal for age* The kidneys had lost in weight relatively less than the body, for they averaged 20 5 per cent above the normal for final body weight, 5 7 per cent below normal for maximum body weight, only 1 per cent below normal for body length, but 19 4 per cent below normal for age In these malnourished children the kidneys had apparently lost in weight relatively more than the brain and perhaps the lungs, but less than any of the other viscera noted

The data for undernourished human adults justify a similar conclusion Bean (1925, 1926) found the kidney weights in 4871 hospital necropsy records 15 per cent higher in the well nourished than in the emaciated In this series as in the malnourished children, the weight of the kidney was depressed relatively less than that of the heart or liver However atrophy of the renal parenchyma during inanition may be masked by the increased blood content, since vascular (especially venous) congestion is a common occurrence

For the lower animals, the observations of numerous investigators indicate that here also during starvation the loss in weight of the adult kidney, though variable, usually averages relatively less than the loss for the entire body In young growing animals, however, the effect on the kidney (as on other organs) varies greatly according to the age and the length or severity of the inanition This is illustrated by the results of the author s experiments on young rats (Figs 14 and 15) In fetuses which had been stunted by [illegible]ncy, the kidneys averaged 6 per [illegible] In rats severely underfed from [illegible] kidneys appeared 90 per cent

above normal, while in rats underfed from birth to ten weeks of age, the kidneys averaged only 38 per cent above normal weight (Stewart) In rats similarly underfed beginning at three weeks of

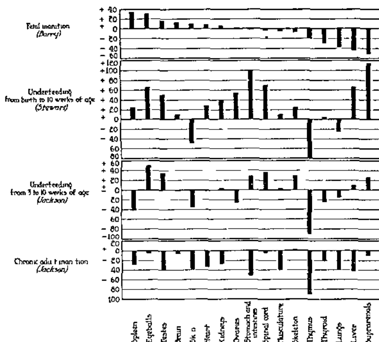


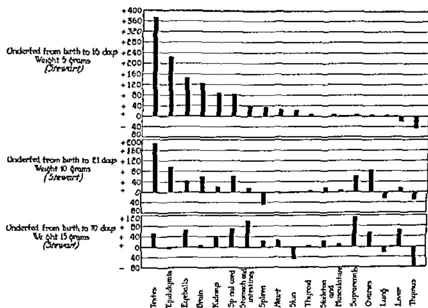
FIG 14 —Chart showing the average relative (percentage) change in the organ

weight The kidney weight has lost 27 per cent or relatively somewhat less than the body weight

age, the kidneys were only 4 per cent above normal (Jackson) In adult rats subjected to acute or chronic inanition, the kidneys

lost about 26 per cent, while the loss in body weight was 33 to 36 per cent (Jackson)

On the other hand, in fasting adult guinea-pigs, at a loss of 20 per cent in body weight, the kidneys had lost only about 5 per cent (Lazareff) At 35 per cent loss in body weight, the kidneys had lost only about 11 per cent, thus appearing very resistant to inanition Numerous other data might be cited from various



F 15 —Chart showing the average relative (percentage) changes in organ weights

observers on different species, indicating that in general the loss in kidney weight during *starvation, though* variable, is always relatively less than that of the body

In albino rats placed on a normal diet after underfeeding from birth or at later periods, Jackson and Stewart *found that the* kidneys within a few weeks had nearly recovered their normal proportionate weight in most cases though sometimes they remained somewhat above normal

Changes in Renal Structure —The numerous studies dealing with structural changes of the kidney during total inanition have been reviewed in detail by Jackson [8] The principal results will be summarized briefly The effects on the kidney, as on other organs, vary considerably according to the species, age and length or severity of the inanition period as well as according to the complications, especially the associated infections

In general it is found that the earlier stages of inanition may cause practically no structural changes in the kidney, excepting perhaps a slight atrophy of the cytoplasm in the renal epithelial



Fig 16 —From a photograph of a section of the kidney in a normal adult albino rat showing two renal (Malpighian) corpuscles and the adjacent cortical labyrinth (chiefly proximal convoluted tubules A normal control for comparison with Fig 17 Zenker fixation hematoxylin-eosin stain × 250 (Jackson The Effects of Inanition and Malnutrition P Blakiston's Son & Co)

cells With more prolonged and severe starvation, the cell atrophy is more pronounced and degenerative changes appear (Figs 16 and 17) Cloudy swelling is often the earliest observed change, followed by granular and fatty or vacuolar cytoplasmic degeneration This degeneration affects primarily and especially the epithelium of the convoluted tubules and sometimes Henle's loop Here, as in other tissues the nucleus is relatively resistant to inanition so that the earlier cytoplasmic atrophy tends to produce an increased nucleus plasma ratio In later stages of degeneration, the nucleus also is involved showing karyolysis or pycnosis, and, finally, fragmentation (karyorrhexis) associated with the terminal

necrosis and disintegration of the cell The desquamated cellular débris may form casts which fill some of the tubules The renal

kidney during inanition is sometimes modified by infections, to which the organism appears predisposed in the generally weakened condition The blood-borne toxic products from the breakdown of



P Blakiston s Son & Co)

tissues throughout the body will also necessarily intensify the renal lesions especially in the later stages of inanition

Jackson[10] has studied the structural changes in new-born rats held at constant body weight for about two weeks by underfeeding The kidneys have nearly doubled in weight They show no degen-

genic zone (normally present in new-born rats) has become reduced with mitoses and developing glomeruli

Relatively few data are available concerning the recovery of normal structure in the kidney through refeeding after a period of total inanition Morpurgo found that in growing rabbits mitoses in the kidney are suppressed by starvation but reappear in large numbers on refeeding Kittelson similarly noted that in underfed new born rats the development of new renal corpuscles ceases On refeeding the renal corpuscles become hypertrophied and increased in number apparently even beyond the normal During inanition the renal cortex is retarded in growth more than the medulla but the normal proportions are soon restored upon refeeding In general it appears that especially in the young the renal lesions occasioned by inanition are as a rule promptly healed upon adequate refeeding

PARTIAL (QUALITATIVE) INANITION

Effects of Partial Inanition Changes in the kidneys have been noted during dietary deficiencies of protein fat mineral salts water and vitamins The earlier literature (Jackson[8, 9]) will be summarized briefly and supplemented by the more recent findings

Protein Deficiency In human famine and allied conditions there is frequently a generalized edema of the body known as famine edema or malnutritional edema While various causes have been suspected the preponderance of evidence including recent experimental work indicates strongly that the most important factor in the pathogenesis of this edema is protein deficiency (Hoelzel 1928 and others)

be ascribed

the kidneys

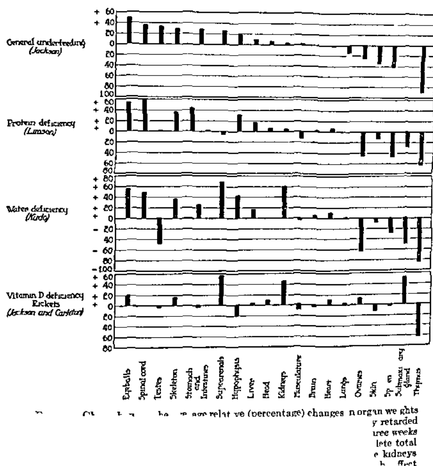
renal struct

account for the edema Some data from the Russian famine were reported by Anitschkoff and Sawodski (1922)

Frisch Mendel and Peters[6] have confirmed Kohman s experimental production of edema in rats by low protein diet but they made no observations on the urinary system Winters Smith and Mendel (1927) found an increase of 55 per cent in the renal weight of young rats held forty days on an inadequate protein diet Wang Huddlestun and Saphir[20] on the contrary found the kidney size proportional to the body size in young rats with arrested or retarded growth on diets deficient in protein The only change noted in kidney structure was frequent cloudy swelling Similarly Jimson and Jackson[4] found nearly normal kidney weight in young rats held at constant body weight for some months by low protein diet (Fig 18) No edema was noted in these experiments

Leiter[3] Barker[1] and Barker and Kirk[2] have produced a variable edema in dogs by plasmapheresis which lowers the serum protein

directly through repeated bleedings rather than by limiting the protein intake According to Barker the urine in these dogs shows albumin fat droplets and renal cell remnants The kidney lesions present a progressive degeneration of the renal tubules



... relative (percentage) changes in organ weights ... y retarded ... ree weeks ... lete total ... e kidneys ... effect

with some destruction of the glomeruli and scar tissue formation The picture suggests nephritis perhaps due to associated infection similar to that frequently found in various types of inanition

Fat Deficiency—Until quite recently it has generally been assumed that fats can be sufficiently synthesized in the organism,

so that a dietary intake of fat is not essential. Earlier unfavorable results on fat free diets were ascribed to shortage of the associated fat-soluble vitamins. McAmis, Anderson and Mendel[15] in rats on extremely low fat but otherwise presumably adequate diets sometimes noted bloody urine, urinary calculi and mottled or pitted kidneys. But eye disorders resembling incipient ophthalmia were also occasionally observed that would indicate the possibility of a vitamin A deficiency in which renal lesions are known to occur. Burr and Burr[4,6] however, working with purified diets adequate except for extremely low fat content discovered a new disorder. This disorder can be prevented or cured by adding small quantities of certain fatty substances including pure fatty acids. The symptoms included a suppression of growth, a peculiar scaliness of the skin and occasional hematuria but no symptoms of deficiency in vitamin A or other known vitamins.

Since the kidneys of Burr's rats at autopsy often appeared grossly abnormal with markedly granular or pitted surfaces, a histological study of the series (total of 75 rats) was made by Borland and Jackson.[3] Although the body weight of the test rats was variably subnormal, the kidneys typically averaged more than 20 per cent above the Wistar norm. The renal surface was pale and granular, sometimes deeply pitted. Degenerative changes appeared to a variable extent in the renal epithelium, more intensive as a rule in the medulla. Atrophy or fatty metamorphosis of the epithelium was often found in both cortex and medulla. Desquamated and disintegrated cells accumulated to form casts, fatty or non fatty, which often filled some of the tubules and especially the papillary ducts. In many cases the degenerating epithelium and casts were calcified, somewhat resembling the condition described by Van Leersum in vitamin A deficiency (to be considered later). In some cases this calcareous degeneration led to extensive necrosis and destruction of the apical region in the renal medulla (Fig. 19). Especially near such areas of necrosis there was also a marked proliferation of the renal pelvic epithelium, forming large irregular masses. This proliferated epithelium however showed no trace of the cornification found in vitamin A deficiency. Slight round-cell (lymphocytic) infiltration occurred in the kidney with about equal frequency in the test rats and apparently normal controls. In only 2 cases polymorphonuclear cells appeared, representing a superimposed infection in the markedly necrotic areas.

The addition of 20 per cent of fat (lard) to the diet almost completely prevented or cured these renal lesions. Even much smaller amounts of various fats appeared highly beneficial, although in some cases marked renal lesions persisted when the general condition of the body had been apparently restored to normal. Thus

the kidney appears to be somewhat more sensitive than the skin or body in general to the effects of a dietary deficiency in fat

Mineral Deficiency —The only data available concerning the effects of mineral deficiency on the kidney are from the experiments of Schultz[17] He found that in rats held at constant body weight (45 gm) for forty days on low salt diet the kidneys increased 63 per cent in weight, while in the controls similarly held constant by low calorie diet the kidneys increased only 14 per cent Sections of the kidney showed no significant changes, although some swollen tubules appeared in both test and control animals

Water Deficiency —The kidneys apparently suffer rather severely from water deficiency, perhaps on account of the associated thicken-

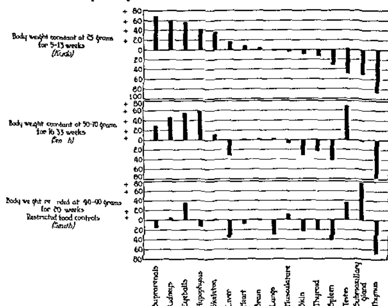


eosin stain (Borland)

ing of the blood, which may impede the circulation Kudo found that while in adult rats on dry diets the loss in renal weight was similar to that during total inanition, in young rats held at constant weight by dry diets the increase in kidney weight (35 to 65 per per cent) was much greater than that during simple underfeeding (Figs 18 and 20) These results were confirmed by Jackson and Smith[11]

Among the earlier observers, Pernice and Scagliosi found in thirsting animals (dog and chick) intense degenerative lesions involving the glomeruli as well as the renal tubules Hyperemia was marked and hemorrhages into the capsular space and tubules were frequent Garofennu and Derevici (1924), in dogs on dry diet, found the glomerular capillaries dilated, with cortical lesions in

advanced cases Kramár[12] and Kramár and Kovács (1927) have made extensive studies of the renal condition in puppies on dry (condensed milk) diet Symptoms of toxicosis appear with albuminuria glycosuria cylindruria and renal lesions The renal lesions which are somewhat irregular and inconstant include hyperemia which is greatest among the straight tubules and fatty infiltration especially in the convoluted tubules



average 1 only 5 per cent above normal

In children on a relatively dry diet (or dry milk potato flour butter and sugar) Schiff and Bayer (192) found a dehydration pyuria Mild albuminuria variable casts leukocytes and red blood cells appeared in the urine Renal abscesses may arise through bacteremia the resistance of the kidneys being reduced by the effects of dehydration Aron (1926) similarly noted that

the kidneys suffer from water deficiency resulting in oliguria or even anuria with urinary casts and leukocytes Any existing pyelitis is aggravated

Since urinary secretion is reduced to a minimum during inanition and especially during thirst it was formerly thought that a study of the finer structure in this condition might throw some light on the much disputed question as to the mechanism of urinary secretion But this hope has not been realized From a study of the kidney of bats during hibernation (where likewise urinary secretion is quiescent) Disse concluded that the brush border of the epithelium in the convoluted tubules represents a resting condition and that it disappears during active secretion Other investigators have failed to confirm this and find no significant change of the brush border during renal secretory inactivity (in hibernation thirst etc) or hyperactivity (experimental diuresis) During the

n

n

shown to be related to the process of secretion The phenomena of the so-called secretion (or resorption) of carmine or other dyes have been studied by Suzuki and others in fasting and thirsting animals but the results are open to different interpretations

Vitamin Deficiencies —It has already been noted that one of the complications of inanition in general is a predisposition to infections in the weakened condition of the organism This lowered resist ance to infections is especially marked as a result of certain vitamin deficiencies Abels designated this characteristic predisposition to infection during avitaminosis as *dysergy* the corresponding structural changes being termed *dystrophy* Both dysergy and dystrophy are found well marked in the kidney during various vitamin defi ciencies

The effects of vitamin deficiency and of other forms of partial inanition often bear a striking resemblance to those of total in anition This similarity of effects in all types of inanition may perhaps be ascribed to the common factor of obstruction to nutri

result of tissue breakdown throughout the body especially in the later stages of inanition In addition to these more generalized effects however each type of inanition produces its own more specific effects probably representing the peculiar disturbances of metabolism occasioned by the deficiencies of the respective indi vidual nutritional elements

McLennan and Jackson[6] found that in adult rats fed a diet deficient in calories but containing the normal requirements in

dietary accessories (proteins, salts and vitamins), resulting in a loss of 40 per cent in body weight, the kidneys lost 26 per cent In another group fed a starch-sugar mixture containing equivalent calories, with the same loss in body weight, the kidneys lost 33 per cent, or about the same as in rats on water alone Thus the presence of the accessory factors seemed slightly to protect the kidney from loss in weight during inanition

Vitamin A Deficiency (Xerophthalmia) — As an example of dysergy, an epidemic of 'spontaneous' nephritis was observed by Jackson in a colony of rats fed on a cereal mixture apparently deficient in vitamin A The eyes showed symptoms of xerophthalmia The kidneys were variable in weight and presented various stages of a focal interstitial nephritis (Figs 21 and 22) with marked round-

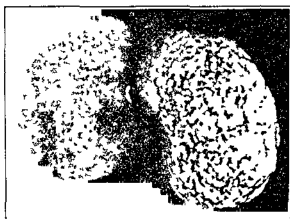


Fig 21 —From a photograph showing the pitted granular surface of an albino rat developing a spontaneous interstitial nephritis on a diet low in vitamin A The smooth surface of the kidney in a normal rat is shown on the left

cell (usually lymphocytic) infiltrations Many renal tubules were

pensatory hypertrophy with weight ultimately doubled or more This increase (which was much greater than the compensatory hypertrophy of the normal kidney) was due partly to general dilation of the renal tubules (Fig 23) Similar infective lesions with multiple renal abscesses were found by Frontali in rats with experimental xerophthalmia on diets deficient in vitamin A A characteristic hyperplasia of the renal pelvic epithelium with more or less cornification, was observed in experimental animals by

Wolbach and Howe Frontali, Fujimaki Van Leersum and Tyso and Smith

One of the most important and striking recent advances in the pathology of nutrition is the demonstration of urolithiasi through vitamin A deficiency Osborne and Mendel discovered urinary or renal calculi in about 10 per cent of their rats on diet deficient in vitamin A while no calculi were found in the control on normal diet This result has been abundantly confirmed by Fujimaki and McCarrison especially in rats on diets deficient in other factors in addition to vitamin A In some cases the vesica calculi (visible by the roentgen rays) disappeared when the animal



... of the kidney cortex showing the struc... es ... th ... n ... s
A depression on the renal surface is shown at the right

were placed on normal diet Similar results were obtained by Van Leersum, Perlmann and Weber, and Tyson and Smith working on vitamin A-free diets

The work of Van Leersum is of especial interest and importance, because he could find no cystitis but traced the pathogenesis of the calculi to the kidney In 88 per cent of his test animals, sections showed numerous small calcareo-fatty granular concretions or casts in the renal tubules and ducts (These somewhat resemble the above-mentioned changes resulting from fat deficiency) He concluded that degeneration of the renal epithelium caused the calcareous deposits and that these were carried to the bladder, where they grew to form the larger concretions Recently Tyson and Smith have likewise noted that renal calculi frequently appear

in rats on low vitamin A diets When obstruction to urinary outflow is present pyonephrosis develops They conclude that there is no metaplasia of the renal pelvic epithelium without infection which is present from the beginning in all cases Furthermore this abnormal epithelium with acute or chronic renal infection may persist following an apparent cure by the addition of vitamin A (in cod liver oil) to the diet



therefore represents largely a pseudohypertrophy

Vitamin B Deficiency (Beriberi Pellagra) —The vitamin B complex is now known to include at least two distinct nutritional factors The first or heat labile factor (B_1 or vitamin F) is the antineuritic or antiberiberi factor which will perhaps continue to be called vitamin B The second or heat stable factor (B_2 P P vitamin I or G) is the more recently discovered growth promoting or antipellagra factor In the earlier work these two factors were not distinguished so but little is yet known as the detailed effects of their individual deficiencies separately

In human beriberi a variable amount of renal parenchymatous degeneration has been reported but usually no signs of nephritis The passive venous congestion so frequently found in the kidney and other organs may perhaps be ascribed to the weakened heart muscle Induy found urinary calculi relatively frequent in malnourished Filipinos especially those with beriberi

Renal disturbance (involving albuminuria hematuria etc) in cases of human beriberi was noted also by Kepler Moore and

especially in young individuals, tends promptly to recover its normal weight and structure, unless the lesions are unusually severe In some cases, however, the renal abnormalities may persist after the body in general has been restored to apparently good condition

References

The titles not included in the following list will be found in the earlier reviews (Jackson, 1925, 1929)

1 Barker M H 1930 A renal lesion following plasmapheresis Proc Soc Exper Biol and Med , 27, 608–609

2 Barker, M H , and Kirk, E J 1930 Experimental edema (nephro-

growth and structure, Philadelphia, P Blakiston s Son & Co

9 ———— 1929 Recent work on the effects of inanition and malnutrition on growth and structure Arch Pathol , 7, 1042–1078; 8, 81–122, 273–315

10 ———— 1932 Structural changes when growth is suppressed by

ts of deficient
53
ion entsprech-
d Wchnschr ,

13 Leiter, L 1928 Experimental edema, Proc Soc Exper Biol and Med 26 173 175

247–262
M 1933 Weights of various
without the dietary accessories,

CHAPTER IX

RENAL COUNTERBALANCE

By FRANK HINMAN, M.D.

Definition.—There are two facts which form the basis of renal counterbalance. These are that the renal mass is divided into two equal portions, a right and left kidney, and that injury or disease usually is circumscribed and only rarely diffuse and uniform, even when bilateral; the majority of renal injuries are unilateral. By counterbalance is meant the anatomical and functional readjustment between the less injured or uninjured portion and the more injured portion in the performance of the total work required. A discussion of this readjustment requires the consideration of renal reserve in relation to the changes of hypertrophy and of atrophy.

EXPERIMENTAL CONSIDERATION OF RENAL COUNTERBALANCE

1. Renal Reserve.—There has been some confusion as to what constitutes renal reserve, and it is a popular conception that the remaining kidney, if normal, is able immediately to take over the extra burden occasioned by removal of its mate. Upon closer consideration this is found to be only partially true and renal reserve is seen to be largely potential and to have both an anatomical and a functional correlation. It is a fact that the renal [illegible] different species of animals is pr[illegible] Small animals [illegible] large kidneys [illegible] f[illegible] tomical reserve [illegible] great many di[illegible] ent observers that [illegible] ed definitely, however, by a [illegible] ent ana[illegible] normal renal mass may be reduced to one-third or even one-fourth by partial resections, and the animal may survive. The remaining kidney substance constitutes the minimal amount of renal mass compatible with life, and it is found that this one-third or one-quarter portion has undergone remarkable hypertrophic changes.

The functional reserve, on the other hand, has been tested experimentally by a study of the function of the remaining healthy kidney after unilateral nephrectomy. We have found that at first this kidney is unable completely to make good the loss of its mate, so that during the first five or six days there is a relative

renal insufficiency This initial insufficiency can be demonstrated also by the results following the ligature of one branch of the renal artery These insufficiencies however, are not proportional to the amount of the renal mass thrown out of action and the insufficiency is removed very quickly by an anatomical hypertrophy of the renal mass remaining Renal reserve thus is seen to be of two types the native reserve which is the normal physiological response to stimulation such as is possessed by all glands and organs and an acquired reserve which is the repair by growth or compensatory hypertrophy in response to overstimulation

2 **Renal Hypertrophy** —Consideration of the changes incidental to renal hypertrophy or repair requires a thorough understanding of the structure of the kidney in addition it is at once necessary to distinguish between renal hypertrophy and renal hyperplasia

though only to a very slight degree up to the fifth or sixth year

take into consideration these two facts In an adult animal s kidney it has been found by careful measurements that growth concerns particularly two structures of the kidney namely the glomerulus and the proximal convoluted tubular area It also has been estimated that from twenty to thirty days usually are required

repair is the result of hypertrophy there are two groups distinguishable—in one the change is by a diffuse mass hypertrophy in the other by a circumscribed or group hypertrophy

An example of mass hypertrophy is the commonly observed unilateral growth of one kidney following removal or loss of its mate Some interesting experiments have demonstrated that this mass type of hypertrophy may be bilateral A typical bilateral mass hypertrophy has been produced by transplantation of one ureter into the duodenum a procedure which throws out as far as actual excretion is concerned the work of one kidney but because this kidney continues to receive the same blood supply it undergoes a compensatory hypertrophy hand in hand with that of its mate

which actually does all of the renal work As seen below, however,

is circumscribed rather
ce in a consideration of
renal counterbalance This type of growth may be tested experi-

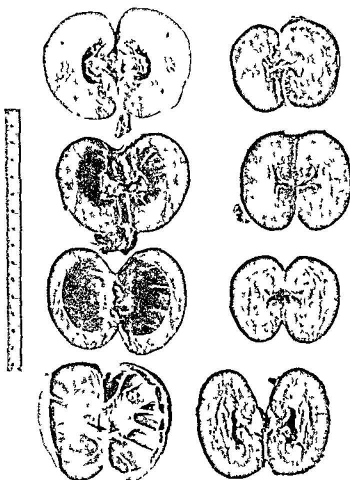


Fig 24 —Closed hydronephroses in dogs of unequal size of seven fourteen thirty and sixty days duration The opposite hypertrophic kidney is shown

mentally by a comparison of the results of three types of repair following relief of ureteral obstruction in hydronephrosis

The distribution in groups of the pathological changes of hydronephrosis gives a reasonable expectation that the less injured groups of glomerulotubular units may recover considerable func-

tional ability after removal of the obstruction The e
to test this is simple Doubly ligate and divide a uret
the bladder as possible so that when the time comes to r
obstruction in order to study repair the end freed of it
can be implanted in the bladder It is found (a) That t
(rabbit cat dog) cannot survive a complete ureteral o
of longer than two to three weeks if the opposite kidney i
at the time of the implantation (b) that a hydronephros
to four weeks duration may repair sufficiently to carry
function with survival of the animal if there is a delay
months between this implantation and removal of the
kidney (c) that a hydronephrosis of thirty to forty days
may undergo sufficient repair to perform the needs of
efficiently if the burden is shifted gradually after ureteral
tion by a slow destruction of the compensatory kidney c
partial obstruction of its ureter

It is found also that functional compensation of the
kidney occurs much more quickly than anatomical comp
which is not complete for from thirty to forty days I
when an anatomical compensatory hypertrophy has occurr
opposite kidney the changes of repair on the hydroneph
(necessarily a hydronephrosis of more than thirty to for
obstruction of the ureter) are reduced to a minimum and
repair is manifested may in time disappear A hydronep
sixty to ninety days duration will show repair nodules
removal of the obstruction but these are functionally n
and will disappear unless given some unusual stimulation
would follow a severe injury to the compensatory mate *

Repair of hydronephrotic atrophy following removal
obstruc
in size
of the
normal appearance The glomerular and convoluted por
these repaired groups will show hypertrophic changes Re
of function will be proportional *not only to the number of st*
units in which repair takes place but also to the degree o
trophy of each With repair the same stage of hydron
destruction will show in different kidneys a variation in th
of these hypertrophic changes according to the nature of th

* ... he ... of renal count

tory burden placed on the kidney at the time the obstruction of the ureter is removed The maximum repair of structure and restoration of function will follow a gradual shifting of the burden such as takes place after the slow destruction of the opposite kidney

3 Renal Atrophy.—Renal atrophy has been regarded almost universally by pathologists as degenerative in type and caused by bacterial chemical or other toxins, producing the well-recognized pathological condition of cloudy swelling and fatty, amyloid and

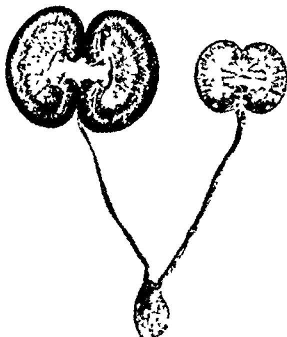


FIG 25—Left unilateral compensatory hypertrophy Right ureter implanted in duodenum for four hundred and forty three days

	Weight gm	Length cm	Width cm	Depth cm
Right	23	5.3	3.9[illegible]	2.05
Left	44	6.0	3.5[illegible]	3.05

hyaline degeneration There is also a well recognized type of atrophy (which may be termed biological) which is caused by inanition, pressure or inactivity and it is possible to produce experimentally what would seem to be a renal atrophy from disuse For instance, the late atrophy following the early repair which takes place upon the relief of obstruction in hydronephrosis of thirty to forty days, when the opposite kidney has been undisturbed and has undergone compensatory hypertrophy during the period of ureteral block

results from insufficient stimulation Another example of atrophy from disuse is furnished by the experiment of ureteroduodenostomy mentioned above in which it was shown that if the animal were examined within sixty to ninety days after the transplantation there was a compensatory hypertrophy of the kidney whose ureter had been transplanted into the duodenum On the other hand if the animal were allowed to survive for a period of two years or more this initial hypertrophy had disappeared completely and the kidney was found to be small almost functionless or completely atrophic The explanation of this late atrophy following an early hypertrophy after ureteroduodenostomy is not altogether clear but it seems reasonable to assume that it results from a gradually diminishing stimulation or loss of work In a successful experiment infection did not occur to produce atrophy, there was no back pressure or ureteral obstruction to cause it and it is doubtful if one might presuppose toxic injury from ascension of the contents of the duodenum into the pelvis of the kidney to cause it Yet atrophy occurred On the other hand it is a well known fact that the activity of the kidney is not continuous and there are periods of inhibition or lessened activity In this experiment whenever the kidney whose ureter was transplanted into the duodenum took a rest period the accumulation of waste substances in the blood was not influenced because the opposite kidney was doing all the work of actual excretion Such rest periods therefore do not lead to any subsequent hyperactivity Any rest period of the com pensatory kidney on the opposite side however must be paid for by an increase of activity later This difference in burden of response with rest and the greater predisposition of the trans planted kidney to inhibition (and rest) would account for the gradual progressive and late atrophy an example therefore of the atrophy of disuse (Figs 26 and 27)

respect to hypertrophy
l equilibrium

ohy following
the complete obstruction of one ureter is so uniformly progressive in like animals of similar weight that for purposes of experiments on repair the same periods of obstruction may be assumed to produce essentially identical degrees of injury (Fig 24)

The compensatory hypertrophy of the opposite kidney is pro gressive and requires thirty to forty five days to become anatomi cally complete It is probable that in this time *the functional* reserve power has not yet reached its maximum

In early stages both the hydronephrotic atrophy and the com pensatory hypertrophy show a markedly *circumscribed distribution* Neither the injury nor the repair is diffuse or uniform

After removal of the obstruction of the ureter, repair of the early stages of hydronephrosis occurs by restoration and hypertrophy of the less injured or uninjured groups of glomerulotubular units Hydronephroses of less than two weeks' duration show a remarkable degree of repair, but in obstructions that have lasted longer than ninety days there is almost no repair

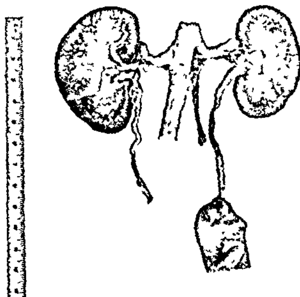


Fig 28 —Right compensatory hypertrophy and left repair two hundred and forty nine days after ureterocystoneostomy for a closed hydronephrosis of twenty one days Relative phenolsulphonephthalein before sacrifice of animal

		Right, per cent	Left, per cent
First appearance in	4 min		8 min
First fifteen minutes		25	5 0
Second fifteen minutes		20	2 5
Total		45	7 5
Kidney weight at necropsy		48 gm	15 gm

No evidence of infection Urine clear without pus or bacteria and sections show no leukocytic infiltration But glomeruli and tubules are small in comparison to those of right kidney This kidney of twenty-one days obstruction is just at the borderline between permanent repair and late atrophy (Compare with Fig 29)

In cases of hydronephrosis of the same degree and duration, the repair which follows removal of the obstruction will vary in proportion to the functional need of repair This need can be modified considerably by injury or removal of the opposite kidney

If the opposite kidney is undisturbed, there will be no permanent

repair following the relief of obstructions of longer than forty-five days and but little after thirty days because the compensatory hypertrophy of the opposite kidney has removed the need for it. The early and rather insignificant repair of a hydronephrosis of thirty days' duration is rarely permanent. Opposite nephrectomy at the same time as the hydroureterocystostomy results fatally in most closed hydronephroses of more than fourteen days' duration, but if the nephrectomy is delayed a few weeks, many dogs with

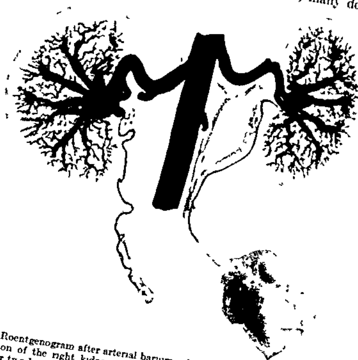


FIG 27.—Roentgenogram after arterial barium sulphate injection showing vascular attenuation of the right kidney whose ureter had been transplanted into the duodenum for two hundred and forty-nine days (shown in Fig 26)

hydronephroses of twenty-one days' duration will survive. If an autonephrectomy is produced gradually by partial obstruction of the opposite ureter, a kidney in which a closed hydronephrosis has existed for thirty to forty days may so repair as to perform total function efficiently (Fig 28). The degree of repair of hydronephrosis after opposite nephrectomy, although the ultimate need for repair is the same, will vary according to whether nephrectomy is performed at the same time, after some delay, or gradually, with an optimum degree of repair in the last instance.

The results of these experiments point to two factors of importance in the control of the growth of the remaining renal units after the loss or injury of others. One is reserve power sufficient

to permit hypertrophy and the other is stimulation of such type and degree as to promote it.

At present we are in no position to explain specifically what constitutes renal stimulation. Blood supply is not fully synonymous though the chemical composition of the blood no doubt plays a rôle. The phenomenon that the different portions of the kidney respond to renal stimulation with different degrees of hyper-



FIG. 8.—Repair of a thirty one-day left closed hydronephrosis (third pair from top in Fig. 4) two years and twenty-six days after partial obstruction of right ureter by stretching a rubber band about it, seven days after the left ureterocystoneostomy. On day of sacrifice total phenolsulphonephthalein first hour 53 per cent, second hour 20 per cent. Urea nitrogen . . . non-protein nitrogen 41 mg. per 100 cc. At necropsy (ether) the right kidney is a large hydronephrotic sac containing 400 cc. fluid with a small remnant of renal tissue at the lower pole. The left pelvis has a capacity of 5 cc. The microscope shows hypertrophy of glomeruli and tubules without infection.

trophy (the proximal convoluted tubules enlarging 60 per cent, the glomeruli 20 and remaining portions less than 10 per cent) is deserving of special consideration. Forced feeding of urea over long periods does not cause this type of hypertrophy, neither does forced diuresis. But the injection into normal dogs of the uremic blood from nephrectomized animals causes a bilateral hypertrophy in every respect analogous to the compensatory growth following unilateral nephrectomy, and double nephrectomy on one of Siamese twins causes hypertrophy of both kidneys in the other. Renal stimulation and renal work are general terms in need of analysis based upon more detailed knowledge of renal physiology. Renal rest can be relative only, never complete. Activity is relative to inactivity for groups of renal units as well as for the unit itself. Periods of rest and of work for each unit have been demonstrated by direct observation, but the concept that whenever a unit works,

it works to full capacity is no longer tenable Though tubular activity is correlated with glomerular work and a glomerulus with its tubular system forms the structural unit of the kidney the functional unit is larger with the blood supply as its basis and comprises a group of structural units with a common blood supply A consideration of the details of the vascularization supports this view All the blood reaching the tubules already has been depleted of certain substances while passing through the glomeruli but the passed to this s loop of one and the same unit might each receive independently blood from different glomeruli Characteristic of the secondary capillary bed are its extensive anastomoses In short each functional unit is a colony of interdependent individuals and the completed work of urine formation is accomplished by the group not the individual

In harmony with these considerations is the occurrence of group atrophy and group hypertrophy and in all renal diseases with group distribution of the injury and of the repair the theory of counterbalance is applicable

CLINICAL CONSIDERATION OF RENAL COUNTERBALANCE

In the application of these experimental considerations the clinical problem is made difficult and uncertain because of our continued ignorance of the mechanism of renal activity, and because of the defects in the clinical estimation of this activity All tests of function are purely empirical and they have the added defect of indicating renal work for the period of the test and for that period only They give no indication of what the kidney has done or will do They are also extremely uncertain guides as to anatomical conditions and because of the incidence of inhibition and hyperpermeability are frequently inaccurate

In addition to function as indicated by these clinical tests the surgeon must estimate the anatomical condition of the kidney This information is furnished by the technical methods of examination Before operation a good idea of the condition of the healthy kidney and of the injured kidney is possible

Renal counterbalance possibly is not of the same significance in the medical diseases of the kidneys as in the surgical But islands of injury and of hypertrophy are found in most types of Bright s disease and the possibility of removing the injury and stimulating hypertrophy deserves consideration The fact that the repair the excep ors of stimulation investigation as do those of injury

of
mt
Fi
kidney is capable of doing Nevertheless, they are of great help when interpreted in the light of our clinical inference in regard to the pathological changes present The application of the theory of renal counterbalance is an attempt on the part of the surgeon to predict the final adjustment of the renal mass which is left after any one of a number of surgical procedures In many conditions, operative treatment is open to serious consideration Sometimes nephrectomy is too radical a conservative procedure being to the best interest of the patient at other times removal of the diseased kidney is the part of good judgment Prescience of the renal mass and of its reserve power and of the type and degree of stimulation it will receive establishes the basis for forecasting the final counter balance after the proposed surgical interference Irrespective of

on each side its relative activity health and reserve power is possible by correlation of a number of clinical and urological facts (1) The history (2) the urine (3) the total renal function (4) the findings of ureteral catheterization as to infection and relative function (5) the size of the kidney shadow in relation to the shape and size of its pelvis (pyelogram) which indicates the amount and thickness of renal parenchyma

These studies aided by other more special ones when indicated give a good clinical estimation of the anatomical and functional condition of each kidney The reserve power and the potentiality of repair may be tested in obstructive conditions by placing retention ureteral catheters for several days and determining if relief of obstruction gives improvement in function If not possible satisfactorily to relieve obstruction by the use of a ureteral catheter preliminary nephrostomy (preferable to pyelostomy) for a few

obstructions, or unilateral ones when the other kidney has been removed previously In a number of cases with only a faint trace of phenolsulphonephthalein excretion in two hours and marked

nitrogen retention (urea nitrogen 300 to 400 mg and creatinine 12 to 14 mg per 100 cc) nephrostomy under spinal anesthesia bilaterally when both kidneys were involved has restored function so that later ureterovesical implantation or other conservative surgery undertaken to relieve the obstruction permanently could be performed successfully Sometimes the plastic repair may be done at the time of the nephrostomy thereby relieving the patient of a second operation A girl with one tuberculous kidney removed the bladder contracted and useless and the other ureter involved and obstructed by the same lesion had a marked renal insufficiency as indicated at the time by no output of phenol sulphonephthalein and a high retention of nitrogen A well functioning nephrostomy tube draining into a rubber urinal fastened to her leg has resulted in considerable renal repair and keeps her free from pain and bladder distress and has enabled her to live for more than three years in comparative comfort Her total phenol sulphonephthalein excretion now averages 30 to 40 per cent

These desperate cases and others like them are clinical proof of the remarkable potentiality of repair of renal tissue when the cause of injury is removed and the need of repair is urgent Conservative surgery should be the rule for all bilateral lesions nephrectomy the exception

In unilateral abnormality repair of lesions anywhere near as advanced as the bilateral ones just mentioned is not to be expected The factors of renal counterbalance explain the apparent discrepancy The good

loss of function in th

support total functio

ould be the rule

exception It is

e must be con

tone is different

of subsequent

involvement of the good kidney is greater and the surgical treatment therefore should be more conservative But it shows poor judgment *to leave as a source of future trouble* badly infected tissue that drains poorly or has pockets of urinary stasis and never would be able to support life alone under any circumstances

The theory of renal counterbalance cannot be formulated into *rules of guidance in these problems* but knowledge of the theory and the factors involved will help in the proper correlation of the clinical and urological facts in surgical conditions

REFERENCE

1 JOELSON J J BECK C S AND MORITZ A R 1929 Renal Counterbalance Arch Surg 19 673 711

PART I

CLINICAL ASPECTS OF RENAL FUNCTION

CHAPTER X

CERTAIN CHEMICAL ASPECTS OF RENAL FUNCTION

By JAMES L. GAMBLE, M.D.

Introduction. The Requirement for Acid-base Control.—We properly regard the essential task of the kidney as consisting in a removal of water and substances from the blood plasma in terms of *the requirement for closely stationary concentrations of the individual* crystalloids in the blood plasma and in the body fluids behind it. In our studies of renal function our admiring curiosity is chiefly focussed on this maintenance of prescribed concentrations. Incidental to this control there is, however, an interesting stipulation, *viz.*, that the reaction of the urine be held within certain bounds. This requirement derives from the circumstance that maintenance of plasma concentrations usually demands removal of plasma base and acid in widely unequal amounts. There is thus obvious need for defensive adjustments to prevent the production of urine at a devastating degree of acidity or alkalinity. This is accomplished by a regulatory mechanism which has been brought into view chiefly by the work of L. J. Henderson. The purpose of *this chapter is to describe the factors of this control and* by *means* of quantitative data display them in actual operation in various situations of acid-base metabolism.

THE ACID-BASE COMPOSITION OF THE BLOOD PLASMA

The relative values of the basic and acid factors are here represented, the former being superimposed in the left-hand and the latter in the right-hand column. It should be noted here that plasma acid must be covered entirely by fixed base, the minute concentration of ammonia permitted being relatively negligible. This circumstance is an important premise in the regulation of acid-base excretion. It should also be mentioned that two of the factors shown in the diagram, the concentrations of protein and of bicarbonate ion (HCO_3), are not directly under renal control. The role

accomplished by the operation together of the two above-described

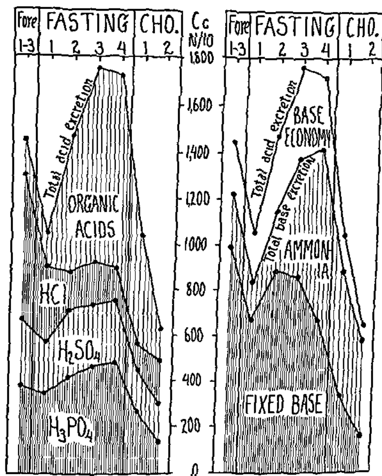


FIG 30 —Illustrating the excretion in urine of a varying excess of acid over fixed base (Gamble J Biol Chem)

illustrate this control These measurements were obtained from consecutive twenty-four-hour urine specimens collected over a three-day foreperiod followed by four days of fasting and a two-day afterperiod during which the only food given was a small amount of carbohydrate in the form of cane sugar The subject was an epileptic boy who was fasted as a therapeutic measure The basic and

acids must be conveyed into the urine. The administration of a small amount of carbohydrate removes this ketosis and also, by its protein-sparing effect, reduces the quantity of other acid radicles and of fixed base presenting for excretion. The conditions of this experiment should therefore extensively exercise the control factors which guard the fixed base level in the plasma.

In the left-hand diagram the four urine acids are shown. Their values are recorded in terms of their base equivalence at the reaction of the blood plasma.* The measurements of the individual acids are superimposed so that the uppermost line describes the total acid excretion. The large extension of the organic acid factor due to ketone acids produced during the period of fasting is evident.

acid values and thus produce a line showing the actual amount of base in the urine. Laying off downward again the values found for ammonia another line is established which describes the fixed-base excretion.† It is apparent from these diagrams that total acid which, while being conveyed to the kidney, must be completely covered by fixed base, is permitted to carry only about one half of its equivalence of fixed base into the urine. The alertness of the control factors in the presence of a developing and

dicated by the peregrinations

excretion. As regards the

ed that direct measurements

of the concentration of fixed base in the blood plasma of this subject demonstrated an accurately sustained value.

RESPONSE OF THE AMMONIA FACTOR IN NEPHRITIS

Discussion of the much debated but still unsettled question as to whether the locus of the regulated production of ammonia is in the kidney or elsewhere will not be undertaken. It may, however, be appropriate briefly to present data which indicate that disease of the kidney is accompanied by a slower than normal response of this factor following ingestion of acid producing salts. These data

* That is, the quantity (0.1 M HPO) found in the urine was multiplied by 1.8 to obtain its base equivalence at the reaction of the blood plasma, and the full value of the measurement of the organic acids was used. The base equivalence of hydrochloric acid and of sulphuric acid is of course the same in urine as in the plasma.

† By way of verification of the proportions on which the construction of these diagrams is based, direct measurements of the fixed base excretion were made and were found to agree closely with the values found by subtracting Titratable Acidity + Ammonia from Total Acid.

are given in Fig 31 They consist in measurements of the increase

noted that the ingested ammonia is not conveyed through the body fluids but is directly after absorption converted into urea so that

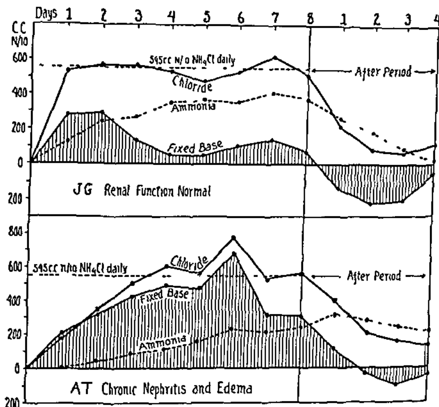


FIG 31 Showing slower response of ammonia factor in the presence of an increase of acid excretion in a patient with nephrosis and edema (lower diagram) as compared with the values found for a normal subject (upper diagram) (Gamble J Clin Invest courtesy of Williams & Wilkins Company)

the ammonia used to cover the excretion of chloride ion must be obtained from urea just as would be the case if the chloride ion were provided by ingestion of hydrochloric acid instead of ammonium chloride The upper diagram describes the findings following ingestion of ammonium chloride by a subject with normal kidneys There is evidently an appreciable lag in extension of the ammonia factor permitting withdrawal of fixed base After a day or two the ammonia increase fairly closely covers the chloride excess and

after the ingestion period it remains elevated and thus permits the loss of fixed base to be rapidly regained. The measurements from which the lower diagram is constructed were obtained from a patient with nephrosis who was edematous. Here the rise in ammonia production is slow and permits a large withdrawal of fixed base which is only to a slight extent regained in the after-period. This loss of fixed base was accompanied by removal of the patient's edema, a presumably desirable event, so that there is here opportunity for debate as to whether the slow response of the ammonia factor represents an adjustment suitable to the circumstances or whether the diuresis should be regarded as obtained by taking advantage of a disabled ammonia mechanism.*

MECHANISM OF THE EXCRETION OF EXCESS FIXED BASE

Having illustrated the operation of the regulatory factors which convey an excess of acid over fixed base into the urine, control of the much less usual reverse situation produced by an excess of fixed base over acid presenting for excretion may now be considered. Obviously the requirement here is for an acid analogue of ammonia, that is, for an acid substance abundantly at hand which can be controllably placed in the urine. Carbonic acid suits these specifications ideally. Its availability is practically unlimited. Routinely it leaves the body base-free by way of the lungs but, when needed, can, *to a regulated extent, be deflected into the urine.*

A study of the carbonic acid and bicarbonate values found in

a simple mechanism.

The concentration

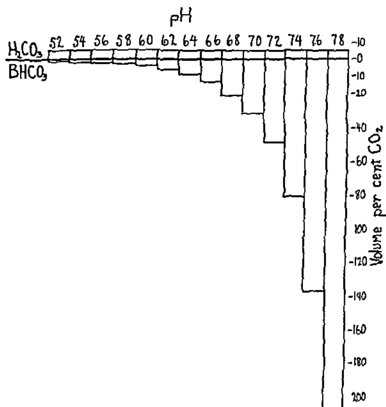
... ... value and is

moreover of approximately the magnitude which obtains in the blood plasma. In other words, the carbonic acid concentration differs strikingly from the concentrations of all of the other substances in urine by remaining in balance with the blood plasma level. As a consequence of the fixed value for carbonic acid, the concentration of bicarbonate in urine becomes a direct function of

* ... ammonia factor.

† Since the hydrogen ion concentration of a solution containing free carbonic acid and bicarbonate is determined by the ratio of the concentrations of the two substances, if one factor remains stationary the other must vary directly with [illegible]. Furthermore the constant value for free carbonic acid produces a fixed value for bicarbonate for each degree of hydrogen ion concentration.

of the blood plasma (7 4) the concentrations of bicarbonate become rapidly *enormous* Evidently we have here the mechanism which establishes the alkaline bound of *urinary reaction* The concentration of bicarbonate which in the presence of the immovable level of carbonic acid would be *necessary to force* the pH of urine above 8 approaches the limit for the total concentration of sub-



stances in t ... l find ng that ... gestion of large amounts of ... alkalinity above pH 8 ...

Another ... diagram is the relatively small quantity of bicarbonate in urine of usual reaction Compare for instance the concentration of bicarbonate at pH 6 with that found in urine of the reaction of blood plasma

pH 7.4. Avoidance of a useless expenditure of base as bicarbonate can, therefore, be recognized as a chief significance of the usual reaction of urine. Insomuch as carbonic acid may leave the body base free by way of the lungs base entering the urine as bicarbonate

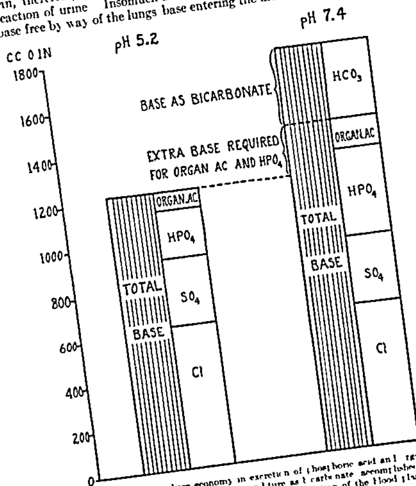


Fig. 31. Illustrating base economy in excretion of phosphoric acid and organic acids and also the prevention of base expenditure as bicarbonate accomplished by the production of urine at pH 5.2 instead of at the reaction of the blood plasma pH 7.4

is obviously completely wasted and such an event in the presence of the usual circumstances of acid base metabolism which demand a conservation of base would be a physiological solecism. The saving of base gained by the excretion of acid instead of alkaline phosphate and of uncombined organic acids has been considered

abo\e This adjustment produces an acid urine and thus mci dentally accomplishes an additional ser\ice to base conser\ation b) almost complete) preventing a large wastage of base as bicar bonate Actuall) the base thus indirectl) conser\ed is a larger quantity than the economy of base obtained in the excretion of phosphoric acid and the organic acids This point is illustrated by the diagrams in Fig 33 which are constructed from measure ments of the four urinar\ acids obtained from a twenty four hour collection of urine The left hand diagram describes their total base equivalence at pH 5 2 which was the actual reaction of the specimen The right hand diagram shows the quantit) of base which the specimen would contain if produced at the reaction of the blood plasma pH 7 4 The extension of the base equi\alence of HPO_4 and of the organic acids at this pH is indicated and also the additional and larger quantit\ of base which would be present as bicarbonate

Although an ordinar\ dietar\ regime produces the requirement for a more rapid remo\al of acid radicles than of fixed base from the pl asma *the re\erse situation demanding defense of plasma aci l* especiall) of its salient factor chloride ion occasionall\ arises From the abo\e discussion of the pH bicarbonate relationship in urine the mechanism at hand is apparent As ma\ be seen by glancing at the diagram in Fig 32 slight increments of urinar\ pH will rapidl) accommodate for the remo\al of base as bicarbonate and relati\el\ huge amounts can be remo\ed within the alkaline bound of urine A diet composed of \egetables and fruits will moderatel\ exercise this mechanism In the case of the herbi\ora it is of course steadil\ in operation The data which are here presented b) wa) of quantitati\e illustration were experimentally obtained but are descripti\e of the situation produced clinically b) the treatment of the state of deh)dration caused b) upper intestinal obstruction The measurements recorded in the dia grams in Fig 34 are from consecuti\e twel\e hour urine specimens obtained b\ catheter from a female dog following an experimental obstruction of the p\lorus *The dog was gi\en as indicated on the* diagram large intraperitoneal injections of ph)siological sodium chloride solution Following obstruction there occurs an extensi\e withdrawal of bod\ fluid caused b) the continued loss of gastric secretions There is also the feature that a deficit of chloride ion is produced which is much larger than the accompan)ing deficit of fixed base (sodium) owing to the relati\ely much greater quantit\ of the former in gastric secretions Consequentl) when sodium chloride solution is gi\en abundantly the deficit of sodium will be repaired long before the loss of chloride ion is replaced and the kidne\ will then be called upon to remo\e sodium and retain chloride ion In the left hand diagram of Fig 34 the measurements of the

acid factors are superimposed and in the right hand diagram those of ammonia and of fixed base are recorded It may be seen that throughout the experiment the chloride-ion content of the urine

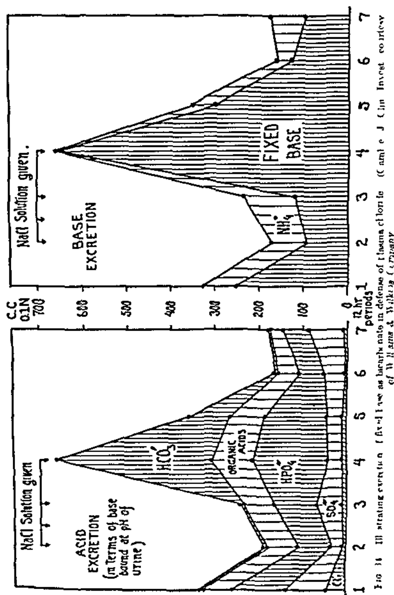
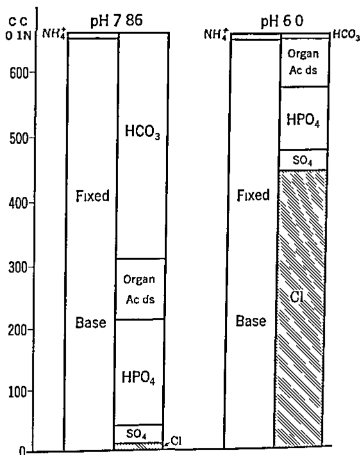


Fig 34 Illustrating excretion of fixed base as bicarbonate in defense of plasma chloride (Gamble J Clin Invest courtesy of Williams & Wilkins Company)

remains minute whereas after the first two injections of salt solution the fixed base excretion rises extensively and in the diagram of acid factors is accompanied by a covering rise of bicarbonate *ion*

The reaction of specimen No 6 which contained most of the bicarbonate was pH 7 8 It is incidentally interesting although



m tan es tl at tl e

plished by the excretion of sodium bicarl onate the ac u ua position of specimen No 6 is given in the left hand diagram of

Fig 35, and in the right hand diagram is shown what would have been the composition of this specimen if produced at a usual urinary reaction pH 6

We thus find that the composition of the blood plasma is admirably defended against the assault of either acid or alkali by mechanisms which are widely extensible and which are capable of operating within the bounds set for the reaction of urine The parts of this defensive machinery are clearly in view They can be seen to adjust themselves with a beautiful alertness and accuracy to rapidly varying situations The secrets however of their motivation and self regulation fortunately remain to be learned

REFERENCES.

1 Gamble J L 1922 Carbonic acid and bicarbonate in urine J Biol Chem 51 295-310

2 Gamble, J L and Ross S G 1925 The factors in the dehydration following pyloric obstruction J Clin Invest 1 403-423

3 Gamble J L Ross S G and Tisdall F F 1923 The metabolism of fixed base during fasting J Biol Chem 57 633-695

CHAPTER XI

THE OPTIMAL WATER REQUIREMENT IN RENAL FUNCTION

By JAMES L GAMBLE, M D

Introduction —The experiments which will here be briefly described represent a very simply devised attempt to learn in approximate terms the quantity of water which best suits the conveyance and excretion in urine of urea and of several salts Progressive increments of these were fed to rats and the corresponding extension of water intake observed Levels of ingestion were reached at which the substances added to the basal diet constituted 90 per cent or more of the total quantity of materials claiming excretion in urine Measurements of the water intake produced by these substances when fed singly or in mixtures may, therefore, be dependably compared A feature of the observations is that they are long-conditioned each measurement being obtained by an experimental period of one week

THE WATER REQUIREMENT FOR SODIUM CHLORIDE AND UREA

The results of a sodium chloride and of a urea experiment are *presented in Fig 36* * *The diagrams in the lower part of the figure* describe the method of providing the intake of these materials

The composition of the basal diet is shown in the first column The essential point is that protein and salt mixture were provided in amounts minimal for satisfactory nutrition in order to keep as low as possible the quantity of materials presenting for excretion in urine besides the added substance Each of the steps in the addition of sodium chloride or of urea represents 1 millimol per gram of food *In the case of the salt the millimol is an "osmolar one, that is each increment was 0 5 millimol of molecular sodium chloride* on the assumption of its practically complete ionization in urine In order to provide the diets with the same caloric value fat was increased and starch decreased appropriately for each dilu*tion of energy caused by addition of salt or urea.* The rats used in all of the experiments were nearly grown males of the same age

* The figures used in this chapter are reprinted with permission from the Am J Phys ol

and closely of the same weight The data from each experiment were produ
containing
and a drinl

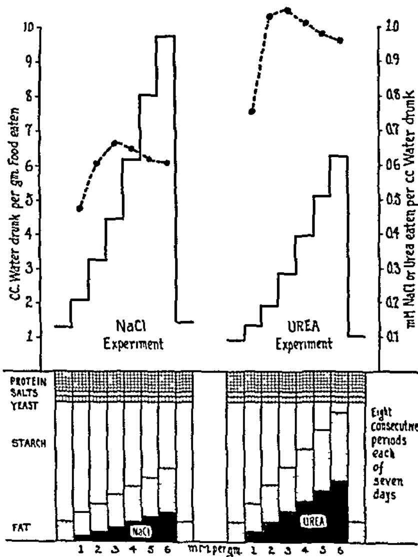


Fig 30

ments of food eaten and of water drunk were made daily The individual periods of an experiment were each of a week's duration

basal measurement The points connected by the broken lines represent the concentration of ingested sodium chloride or urea in

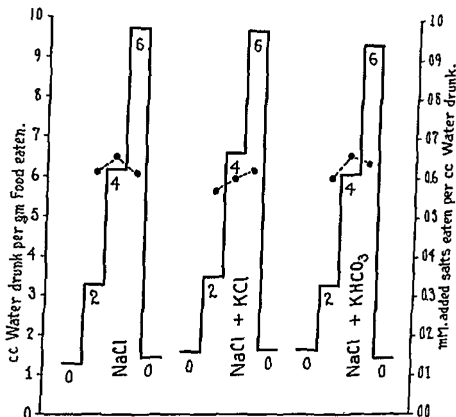


Fig 37

terms of the accompanying water intake In both experiments, when the food contains 2 or more millimols of added substance per gram, these values are established at fairly stationary levels that for sodium chloride being approximately 0 6 M (osmolar), whereas for urea a much higher value, approximately 1 M is found It is quite clearly the evidence of these data that the optimal water requirement for the conveyance and removal in urine of ingested sodium chloride is much larger than for equivalent amounts of urea

THE WATER REQUIREMENT FOR MIXTURES OF SALTS

The diagrams in Fig 37 present for comparison with the data found for sodium chloride those obtained by adding to the diet mixtures of equal parts of sodium chloride and potassium chloride and of sodium chloride and potassium bicarbonate In these experiments the food contained per gram 2 4 and 6 millimols of added materials in the three successive periods As may be seen in the diagrams the levels of water-drinking produced by the salt mixtures and also the concentration values in terms of the water intake agree closely with those of the sodium chloride experiment It is therefore evident that the optimal water requirement produced by these several salts is identical or nearly so Since this finding was obtained by using mixtures of the salts the additional information that the individual requirements are additive is gained

THE WATER REQUIREMENT FOR MIXTURES OF UREA AND SALTS

As has been noted (Fig 36) the optimal water requirement for urea is less than obtains for these salts This fact did not disturb an expectation that the requirements for salts and for urea would be found to be additive The results of two experiments undertaken to test this point are presented by means of the diagrams in Fig 38 The first column represents the water intake per gram of food when it contains 2 millimols of potassium chloride per gram The next column measures the water intake in a diet containing 2 millimols of urea per gram The water intake in a diet containing 4 millimols of added material composed of 2 millimols of potassium chloride and 2 millimols of urea is shown by the third column The expected height of this column on the assumption that the individual water requirements are additive is shown by the broken line and the expected concentration of the mixture of ingested substances referred to water intake is indicated by a circle The actual height is interestingly approximately double that of the urea column that is it has the value which would be expected if the added 4 millimols of material were entirely urea and in consequence the concentration value found for the mixture of potassium chloride and urea referred to water intake is about the same as for urea alone Repeating the experiment using larger quantities of the substances gave as may be seen in the second section of the figure identical results

Conclusions The results of these simple experiments with rats consisting in measurements of the voluntary water intake accompanying increments of materials placed in a basal diet demonstrate (1) That the optimal water requirement for removal in urine of each of several salts studied (NaCl KCl and $KHCO_3$)

is identical or nearly so and that the individual requirements are, at least closely, additive, (2) that the quantity of water required for removal of urea is much less than for corresponding osmolar amounts of the salts, (3) that the differing requirements for urea and the salts are not additive, the requirement for a mixture of equal amounts of urea and salt being approximately the same as for an equivalent quantity of urea alone

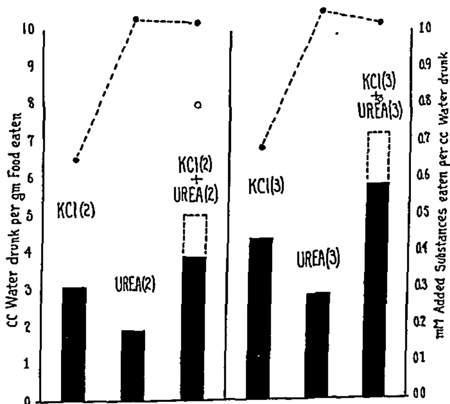


FIG 38

The significance of the sum of these findings may be described as indicating an economy of water in renal function referable to urea *

... detail and by measure- ... F Butler A ... referable to

REFERENCE

... 1929 The optimal ... water drinking by ... in the food, Am J Physiol, 88, ...

CHAPTER XII

THE NON-EXCRETORY FUNCTIONS OF THE KIDNEY

By ISIDORE SNAPPER, M.D.
AND
ALFRED GRÜNBAUM, CHEM.D.

CONJUGATION BY THE KIDNEY

THE excretory function of the kidney is usually considered as its only function. It must indeed be its main one because nearly all urinary substances are also found in the blood without being formed in the kidney. Such is the case with urea, uric acid, sodium chloride, almost surely with creatinine and many other urinary constituents.

One instance of a different category of processes has been known for more than half a century. In a classical perfusion experiment on the excised kidney of a dog, Bunge and Schmiedeberg[2] showed that chemical synthesis takes place in the kidney: benzoic acid (C_6H_5COOH) and glycine added to the perfusion blood were linked in the kidney to form hippuric acid, which was recovered from the perfusion fluid after one to two hours had elapsed. Detailed studies of this synthetic function formed the starting point from which followed the discovery of the oxidative functions of the kidney.

The importance of their discovery was increased when Bunge and Schmiedeberg showed that, as far as the dog is concerned, the synthesis of the hippuric acid takes place in the kidney only. If sodium benzoate and glycine were injected in the circulation of nephrectomized dogs, no hippuric acid could be demonstrated in the blood or organs of these dogs. Some years ago Kingsbury and Bell[12] challenged these results. They did not deny that the kidney was able to perform the synthesis of hippuric acid, but they maintained that after injection of sodium benzoate and glycine in nephrectomized dogs hippuric acid could be detected in the blood and in the liver. It is of vital importance for this question to point out that Kingsbury and Bell did not demonstrate the presence of hippuric acid; they showed the presence of benzoic acid conjugated with other substances, but did not prove that hippuric acid was formed. The authors[21] have several times repeated Bunge and Schmiedeberg's experiment and have not been able to find hippuric acid in the blood after injection of sodium

benzoate and glycine in the circulation of bilaterally nephrectomized dogs The classical experiment of Bunge and Schmiedeberg still prevails in the dog the kidney is the only organ which is able to form hippuric acid

As pointed out by Bunge and Schmiedeberg there are other animal species for instance the frog and the rabbit where the kidney is unable to synthetize hippuric acid In these animals it is probably the liver which has the power to bring about this synthesis[9]

It had never been proved that the *human* kidney is able to form hippuric acid Using kidneys obtained by operation the authors were able to demonstrate that the human kidney is capable of this synthesis Before the operation the function of (tumor) the kidney to be removed was shown by cystoscopic examination to be only slightly damaged Immediately *after operation the perfusion* took place Human blood to which sodium benzoate and glycine

synthetic and not merely excretory functions

lney func

tı had been

fo ouric acid

excretion is disturbed Investigating this problem[23,24] we found a parallelism between the ab

containing substances and it t

remained an open question f

sodium benzoate does not bring about the normal increase in the excretion of hippuric acid whether the low excretion is due to diminished synthesis or to retention The authors were able to demonstrate that in cases where excretion of hippuric acid is almost completely inhibited synthesis takes place all the same To patients in uremia with impaired hippuric acid excretion 15 gm

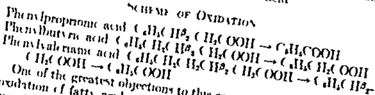
hippuric acid along with other nitrogenous waste products formed but is not excreted Thus the hippuric acid tests in kidney diseases run parallel with and are to be considered in the same category as other nitrogen excretion tests

After ingestion of the homologa of benzoic acid characteristic conjugation products appear in the urine When phenylacetic acid ($C_6H_5CH_2COOH$) the first homologon of benzoic acid (C_6H_5

COOH) is ingested or subcutaneously administered the corresponding glycine compound, phenaceturic acid, is formed and excreted. Perfusion experiments with isolated mammalian kidneys showed that this synthesis can be accomplished by the kidney, considerable quantities of phenaceturic acid were recovered from the perfusion blood.

OXIDATION BY THE KIDNEY

The fate of the higher homologs of benzoic acid, the aromatic fatty acids, is of importance primarily for our knowledge of fat metabolism since the complete oxidation of the aliphatic fatty acids to CO_2 and water made difficult any insight into the mechanism at play. Upon the isolation of the oxidation products of the aromatic acids rests our knowledge of fat metabolism. Knoop demonstrated that any higher homologon of benzoic acid possessing an odd number of carbons in the chain is oxidized to benzoic acid (which may be considered as phenylformic acid C_6H_5COOH) and is excreted as hippuric acid and any homologon with an even number of carbons in the chain is oxidized to phenylacetic acid and excreted linked with glycine as phenaceturic acid.


SCHEME OF OXIDATION

Phenylpropionic acid $C_6H_5CH^{\beta}_2CH_2COOH \rightarrow C_6H_5COOH$

Phenylbutyric acid $C_6H_5CH_2CH^{\beta}_2CH_2COOH \rightarrow C_6H_5CH_2COOH$

Phenylvaleric acid $C_6H_5CH_2CH_2CH^{\beta}_2CH_2COOH \rightarrow C_6H_5CH^{\beta}_2\text{-}CH_2COOH \rightarrow C_6H_5COOH$

One of the greatest objections to this conception was the fact that oxidation of fatty acids in vitro never had been observed to occur via β-oxidation. Dakin, however, has proved that by gentle oxidation of fatty acids with hydrogen peroxide the products of β-oxidation can be isolated in vitro.

Shortly after Knoop's publications, bedside experiments of Sasha and Schwarz with diabetic patients showed that β-oxidation of normal fatty acids increases ketosis.

Finally, Embden and his school proved by direct perfusion of the liver with blood to which fatty acids were added that the chains of aliphatic acids with an even number of carbon atoms are shortened in the liver by β-oxidation to butyric acid, which is partially oxidized, yielding β-hydroxybutyric acid as a result of the perfusion experiments. It had not yet been possible to prove any corresponding oxidation of the aromatic acids by the liver, though the β-oxidation of the aromatic acids by the intact organism was amply demonstrated by Knoop.

In perfusion experiments on the isolated mammalian kidney the authors obtained results analogous to those of Knoop. Perfu

sion of the kidney of sheep and calves with glycine and phenyl

of the kidney was demonstrated

In later (unpublished) experiments it was found that the kidneys of Carnivora (dog) are not identical with those of Herbivora (sheep and calves) in their oxidative capacity The authors demonstrated that the kidney of the dog oxidizes phenylpropionic acid ($C_6H_5CH_2$ CH_2COOH) only to cinnamic acid ($C_6H_5CH = CHCOOH$) if one perfuses the kidney of a dog with blood to which phenylpropionic acid and glycine have been added the urine excreted during the experiment contains consider

i e a substance which consist

Cinnamic acid is formed fro

tion of two hydrogen atoms

to be considered an oxidation as demonstrated by Wieland for

Per

d and

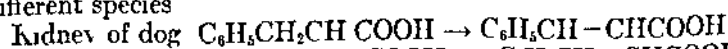
glycine gives rise to the formation of cinnamoylglycine and not hippuric acid

Phenyl β hydroxy propionic acid ($C_6H_5CHOH\ CH_2COOH$) is hardly attacked by the isolated kidney of the dog only minute amounts of cinnamoylglycine are formed

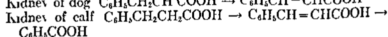
It has been pointed out by Dakin [3] and especially by Quick [17] that cinnamic acid may be the first stage in the β-oxidation of phenylpropionic to benzoic acid If this is the case then the kidney of the dog is able to bring about this first step and the *complete oxidation of phenylpropionic acid to benzoic acid* must take place in another organ In confirmation the authors proved that the isolated liver of a dog can form benzoic acid if the organ is perfused with blood to which phenylpropionic acid or cinnamic acid or phenyl β hydroxypropionic acid is added

The oxidation of phenylpropionic acid in the β CH_2 group to benzoic acid in the kidneys of the calves and sheep may also take

scheme for the β-oxidation of phenylpropionic acid in the kidney of different species



Kidney of dog $C_6H_5CH_2CH\ COOH \rightarrow C_6H_5CH-CHCOOH$



Kidney of calf $C_6H_5CH_2CH_2COOH \rightarrow C_6H_5CH=CHCOOH \rightarrow$ C_6H_5COOH

It is important to remember that the kidney is not the only organ in which β-oxidation occurs The liver too is certainly capable of performing β-oxidation and as a result of this process large amounts of β hydroxybutyric acid are formed The explanation is that through this type of oxidation butyric acid is formed from the naturally occurring fatty acids with their long chains of carbon atoms in even numbers and by the action of the liver butyric acid is partially oxidized to β hydroxybutyric acid (Fatty acids with carbon chains of uneven numbers give rise to propionic acid and propionic acid perfused through the liver disappears completely) Still under normal conditions the β hydroxybutyric acid content of the blood is insignificant and in normal urine β hydroxybutyric acid or other ketone body can scarcely be detected So we must conclude that in the normal organism considerable quantities of β hydroxybutyric acid formed by the liver must disappear

In current literature one always reads that the liver (see Wakeman and Dakin[3] and Marriott[15]) is able to oxidize β hydroxybutyric acid This is correct only to a certain extent because during this oxidation only aceto-acetic acid and acetone are formed both products which like their mother substance are never found in normal body fluids This partial oxidation of β hydroxybutyric must not be confused with the process by which the animal body gets rid of the large quantities which must be formed during fat metabolism Partial oxidation similar to that occurring in the presence of liver cells has been shown to be reversible in the presence of normal tissue (von Lagermark[34])

The solution of the question was difficult because of the inadequacy of our methods of determining traces of β hydroxybutyric in tissues The technique of Engfeldt and Van Slyke can hardly be used for this purpose because of the interference of lactic acid and other substances The authors have devised a method [5] suitable for this purpose and have been able to determine the fate of β hydroxybutyric acid in the liver

They found[26] that during the perfusion of liver with blood to which β hydroxybutyric acid was added this substance was not converted to CO_2 and water We confirmed the work of other workers that during perfusion it is oxidized to aceto acetic acid Calculations show that the entire amount which has disappeared is transformed into aceto-acetic acid It is important to take into account the quantity absorbed by the liver cells during the trans

further oxidized during perfusion through the liver Some is reduced to β-hydroxybutyric acid and some is absorbed by the

sion of the kidney of sheep and calves with glycine and phenylpropionic ac
rnanic acid
acid, as wa
of the kidney was demonstrated

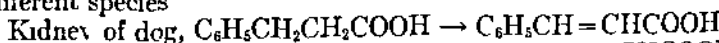
In later (unpublished) experiments it was found that the kidneys of Carnivora (dog) are not identical with those of Herbivora (sheep and calves) in their oxidative capacity. The authors demonstrated that the kidney of the dog oxidizes phenylpropionic acid ($C_6H_5CH_2$-CH_2COOH) only to cinnamic acid ($C_6H_5CH = CHCOOH$) if one perfuses the kidney of a dog with blood to which phenylpropionic acid and glycine have been added the urine excreted during the experiment contains considerable amounts of cinnamoylglycine, *i e* a substance which consists of cinnamic acid linked to glycine Cinnamic acid is formed from phenylpropionic acid by subtraction of two hydrogen atoms This formation of cinnamic acid has to be considered an oxidation as demonstrated by Wieland for

Per-
id and
glycine gives rise to the formation of cinnamoylglycine and not hippuric acid

Phenyl-β-hydroxypropionic acid ($C_6H_5CHOH CH_2COOH$) is hardly attacked by the isolated kidney of the dog, only minute amounts of cinnamoylglycine are formed

It has been pointed out by Dakin[3] and especially by Quick[17] that cinnamic acid may be the first stage in the β-oxidation of phenylpropionic to benzoic acid If this is the case then the kidney of the dog is able to bring about this first step and the complete oxidation of phenylpropionic acid to benzoic acid must take place in another organ In confirmation, the authors proved that the isolated liver of a dog can form benzoic acid if the organ is perfused with blood to which phenylpropionic acid or cinnamic acid or phenyl β hydroxypropionic acid is added

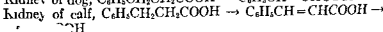
The oxidation of phenylpropionic acid in the β CH_2 group to benzoic acid in the kidneys of the calves and sheep may also take
namic
d
s
i-
g



scheme for the β-oxidation of phenylpropionic acid in the kidney of different species

Kidney of dog, $C_6H_5CH_2CH_2COOH \rightarrow C_6H_5CH=CHCOOH$

Kidney of calf, $C_6H_5CH_2CH_2COOH \rightarrow C_6H_5CH=CHCOOH \rightarrow$


CH

It is important to remember that the kidney is not the only organ in which β-oxidation occurs The liver too is certainly capable of performing β oxidation and as a result of this process large amounts of β hydroxybutyric acid are formed The explanation is that through this type of oxidation butyric acid is formed from the naturally occurring fatty acids with their long chains of carbon atoms in even numbers and by the action of the liver butyric acid is partially oxidized to β hydroxybutyric acid (Fatty acids with carbon chains of
acid and propionic acid p
completely) Still under nc
acid content of the blood is insignificant and in normal urine β hydroxybutyric acid or other ketone body can scarcely be detected So we must conclude that in the normal organism considerable quantities of β hydroxybutyric acid formed by the liver must disappear

In current literature one always reads that the liver (see Wakeman and Dakin[35] and Marriott[6]) is able to oxidize β hydroxybutyric acid This is correct only to a certain extent because during this oxidation only aceto acetic acid and acetone are formed both products which like their mother substance are never found in normal body fluids This partial oxidation of β hydroxybutyric must not be confused with the process by which the animal body gets rid of the large quantities which must be formed during fat metabolism Partial oxidation similar to that occurring in the presence of liver cells has been shown to be reversible in the presence of normal tissue (von Lagermark[34])

The solution of the question was difficult because of the inadequacy of our methods of determining traces of β hydroxybutyric in tissues The technique of Engfeldt and Van Slyke can hardly be used for this purpose because of the interference of lactic acid and other substances The authors have devised a method[5] suitable for this purpose and have been able to determine the fate of β hydroxybutyric acid in the liver

They found[26] that during the perfusion of liver with blood to which β hydroxybutyric acid was added this substance was not converted to CO_2 and water We confirmed the work of other workers that during perfusion it is oxidized to aceto acetic acid Calculations show that the entire amount which has disappeared is transfo
account t
fusion
erroneous
liver perf
further oxidized during perfusion through the liver Some is reduced to β hydroxybutyric acid and some is absorbed by the

liver tissue Therefore, the great quantities of β hydroxybutyric acid which must be formed during metabolism cannot be split up by the liver

In view of the enormous oxidative capacity of the kidney which the authors had found in their previous experiments in which they showed that this organ is able to oxidize the resistant phenylbutyric acid to phenylacetic acid it seemed more than probable it is able to bring about oxidation of β-hydroxybutyric acid to smaller complexes and eventually to CO_2 and water During perfusion of the kidney with blood to which β-hydroxybutyric acid was added, not the slightest trace of aceto-acetic acid could be detected, though the greatest part of the β hydroxybutyric acid had disappeared[31] Similarly aceto-acetic acid re-fore, we have to consider t to destroy the great quantitie to-acetic acid

Are the

Evidently

oxidizing ketone bodies

Summarizing one must conclude that *the ketone bodies are* formed in the liver and are oxidized in the muscles and kidneys

THE RÔLE OF THE KIDNEY IN CERTAIN INSTANCES OF DIABETES MELLITUS

How is this oxidative power of the kidney and the muscles influenced by diabetes? Everyone knows that in diabetes mellitus the accumulation of β hydroxybutyric and aceto acetic acid in the body fluids is one of the greatest dangers which threatens the diabetic patient What is the mechanism by which these ketone ? It is well known

has become a volcano which spreads great quantities of β ketone bodies would kill coma if there were no kidney and muscles

To determine whether the muscles of dogs suffering from phlorhizin diabetes and severe acidosis retain undiminished capacity of oxidizing ketone bodies the authors perfused[30] the kidneys and hind limbs of such animals adding β hydroxybutyric acid to the perfusion fluid As the result of their experiments it appears that the kidneys and the muscles of the acidotic animals oxidize considerable quantities of ketone bodies Thus they concluded that the oxidative functions of the kidneys are not primarily disturbed as an integral part of the diabetic alteration of metabolism

What then is the relation of the kidney to diabetic coma? The acidosis of phlorhizin diabetes is evidently caused by the over production of ketone bodies by the fatty degenerated liver while kidneys and muscles are working hard to oxidize the enormous quantities of ketone bodies A certain part of these hyperproduced substances cannot be oxidized even by the maximal function of kidney and muscles these are the circulating ketone bodies which cause the acidosis of the phlorhizin diabetic dog

The condition of the diabetic patient then is partially dependent on the condition of his kidneys As long as the latter are functioning normally as is the case in acute phlorhizin diabetes and most instances of diabetes mellitus the acidosis is kept within reasonable limits When the catastrophe of diabetes occurs beginning with a complete breakdown of the glucose tolerance and a greatly increased production of ketone bodies and ending in coma there are at the beginning at least three different mechanisms at play by which the kidney combats the acidosis *viz* excretion of ketone bodies oxidation of ketone bodies and increased ammonia production In certain cases of severe diabetes mellitus which cannot be saved by insulin these functions break down and degeneration of the kidney is not infrequently observed The following signs of damaged kidneys are known to occur in coma [19 20] (*a*) Decreased

numbers (*d*) albuminuria when independently present varying with the degree of acidosis and (*e*) (Van Paasen[33]) impaired power of ammonia formation during and after coma

That the various functions of the kidney are not independent but produce an additive strain on the kidney may be argued from the reaction of the kidney to Petren s diet This diet in which such large amounts of fats are given can be endured only if the amount of protein administered at the same time is maximally restricted The withdrawal of nitrogen-containing foodstuffs apparently eases the burden on the kidney thereby increasing its oxidative power so that it is able to cope with the hyperproduction

of ketone bodies arising from Petren s diet As a matter of fact as soon as proteins are added to Petren s diet coma may be imminent

Evidently then the renal insufficiency in diabetes must be a special one because oxidative as well as excretory functions are impaired It must not be identified with the renal insufficiency of *glomerulonephritis where only damage of* excretory functions can be demonstrated

In the majority of cases where the kidneys are healthy coma appears only if *the quantities of β-hydroxybutyric acid (formed* especially after an unreasonable diet) are so enormous that even the normal kidneys and muscles cannot handle this hyperproduction These coma cases are cured by insulin *In two groups of* patients in diabetic coma the administration of insulin does not bring about recovery one consists of older individuals with arteriosclerotic changes the other consists of individuals in whom the acid

kidneys may play a role in the outcome

Much interest has been given to the kidney lesions in diabetic coma Some writers (Van Paasen[33] Metzger[16]) have found only small and insignificant lesions in the coma kidney Others have described (Warburg[36] Ehrmann[5]) (*a*) Hyaline degeneration of the descending part of Henle s loop (Armanni) (*b*) glycogen degeneration (Ehrlich) (*c*) coagulation necrosis of tubuli contorti (Weigert) and (*d*) fatty degeneration of epithelia of the tubules

Summary —1 The oldest known non-excretory function of the kidney *i e* the formation of hippuric acid is also performed by human kidneys

2 Formation of phenaceturic acid *i e* the binding of phenyl acetic acid with glycocoll *also takes place in the kidney*

3 β-oxidation of phenylpropionic acid to benzoic acid β oxidation of phenylbutyric acid to phenylacetic acid β-oxidation of *phenylvalerianic acid to benzoic acid are easily performed by* the isolated kidney of the calf and the sheep

4 Considerable quantities of β hydroxybutyric acid and aceto-*acetic acid are destroyed by the isolated kidney*

5 Also the muscles but not the liver are able to destroy ketone bodies

6 In acute ketosis (phlorhizin diabetes) kidney and muscles have still retained the power of destruction of ketone bodies

7 It is not improbable that in *some* cases of human diabetes impaired destruction of ketone bodies in the kidney may be one of the causes of ketosis

8 The β-oxidation of the aromatic fatty acids is different in the kidney of different animals

In the kidney of the dog only a Wieland oxidation of phenyl propionic acid takes place whereby cinnamic acid is formed This cinnamic acid is linked with glycine by the kidney to cinnamoylglycine

The kidney of the dog is not capable of oxidizing cinnamic acid to benzoic acid

9 However the kidney of the calf and the sheep oxidizes not only phenylpropionic but also cinnamic acid readily to benzoic acid

10 These facts enhance the probability that the oxidation of phenylpropionic acid to benzoic acid in the kidney takes place *via* the formation of unsaturated cinnamic acid The kidney of the dog is then only capable of performing the first stage of this oxidation of phenylpropionic acid *i e* formation of cinnamic acid The kidney of the calf oxidizes the phenylpropionic acid first to cinnamic acid and then to benzoic acid

11 The liver of the dog is also capable of oxidizing phenyl propionic acid cinnamic acid and phenyl β hydroxypropionic acid to benzoic acid (β oxidation in the liver)

REFERENCES

1
2
purs u
3
phenyl
4
London
5 EHRMANN R AND JACOBY A 1925 Ueber Blutungen bei mit Insulin behandelten Komafallen Klin Wchnschr pp 2151 2153
6 ELMER A W AND SCHEPS M 1928 Beitrage zur Kenntnis und

10 GOTTSCHALK A AND MÜLLER O 1930 Funktionsstorungen der
204 1207
hsel und Acidosis Handb
iann 5 605–6 0
The synthesis of hippuric
-301
Hofmeister's Beitr 6 150–162 er Fettsäuren im Tierkorper
14 ———— 1908 Zur Oxidation von Fettsäuren Hofmeister's Beitr 11 411–414
15 MARRIOTT W McK 1914 The metabolic relations of the acetone substances 18 241 26
16 METZGER H 19 Ueber Nierenbefunde beim Coma diabeticum Med Klin 23 598
17 QUICK A J Quantitative studies of β-oxidation J Biol Chem 80 515–526

18 Schwartz, I 1903 Untersuchungen uber Diabetes, Deutsch Arch f klin Med, **76**, 233–289

19 Snapper, I 1927 Niere und Coma diabeticum, Med Klin, **23**, 897–900 and 1897–1898

20 ———— 1928 The rôle of the kidney in non renal disorders, Proc Roy Soc Med, **21** (1), 1230–1233

21 Snapper, I, and Grunbaum, A 1924 Ueber die Hippursauresynthese in der uberlebenden Niere von verschiedenen Tiergattungen, auch vom Menschen, Biochem Ztschr, **145**, 40–46

22 ———— 1924 Ueber die β-Oxidation in der Niere, Biochem Ztschr, **150**, 12–17

23 ———— 1924 Der Hippursaurestoffwechsel bei Nierenkrankheiten Klin Wchnschr, **1**, 101–104

24 ———— 1926 L excrétion de l acide hippurique dans les affections rénales, Presse méd, **34**, 1524–1526

25 ———— 1926 Ueber die Methodik der β Oxybuttersaurebestimmung in Leber und Muskeln, Biochem Ztschr, **175**, 357–365

26 ———— 1927 Ueber den Abbau der β Oxybuttersaure in der Leber, Biochem Ztschr, **181**, 410–417

27 ———— 1927 Ueber den Abbau der Diacetsäure in der Leber, Biochem Ztschr, **181**, 418–424

28 ———— 1927 Ueber den Abbau der Diacetsaure in der Niere, Biochem Ztschr, **185**, 223–228

29 ———— 1928 Ueber den Abbau von Diacetsaure und β-Oxybuttersaure in den Muskeln, Biochem Ztschr, **201**, 464–472

[illegible]

36 Warburg, E 1925. Diabetic coma with uremia, Acta med Scand, **61**, 301–334

CHAPTER XIII

THE PHENOLSULPHONEPHTHALEIN AND OTHER TESTS OF RENAL FUNCTION

By LEONARD G ROWNTREE, Sc D , M D

Introduction.—The history of the phenolsulphonephthalein test is of interest because it is the story of our first success in the investigation of the function of the kidney in disease This procedure which has stood the test of time, was responsible for the conversion of the medical profession to a new idea It demonstrated both the importance and the practicability of determining the functional capacity of the kidney in disease

A tale of more than ordinary interest is told of Ira Remsen, formerly president of the Johns Hopkins University, who in his youth sponsored the birth of phenolsulphonephthalein Toward [illegible]

[illegible]

inquired as to the nature and purpose of this test He was informed that the findings would determine whether or not he would have the operation On further inquiry, he learned that it was the phenolsulphonephthalein test [illegible] quirks, a substance which he [illegible] youth was being used in his ol[illegible]

Until 1909, renal function tests played but an unimportant rôle in the surgical examination of the patient and practically no rôle in the medical examination Desultory studies had been carried on from time to time in some of the larger clinics, especially abroad, but the subject had not attained true clinical importance The prevailing viewpoint of that period may be grasped from a leading medical authority who in the year 1910 says "So far as our power of determining the functionating capacity of the two kidneys is concerned, I think we must rely upon an examination of the urine by means of the older and simpler methods *i e*, examination for [illegible]

disease The results, of course, are not always reliable They can,

perhaps in questionable cases be made more accurate by using the phlorizin test

The author's interest in the phthaleins was created by Prof John J Abel In 1908 the author had the privilege of collaborating with him in a study of the pharmacological action of some of the phthaleins and their derivatives with reference to their behavior as purgatives the phthaleins being supplied by Remsen and by Orndorff Our problem was to find a good subcutaneous purgative Our most important findings however were (1) The low toxicity of various phthaleins (2) their laxative action particularly of the tetrachlor derivatives and their excretion through the bile and (3) the rapid elimination of the phenolsulphonephthalein by the kidney

An effort was therefore made to determine whether phenolsulphonephthalein was better adapted as a functional test for the kidney than other substances already tried This involved the application of the test to clinical cases and thus Dr Geraghty came into the study He was a surgeon of outstanding ability a keen observer and indefatiguable investigator and as true a friend and as fine a collaborator as ever a man could wish Association with him was not alone a pleasure but from the standpoint of our work a matter of extreme good fortune Scientifically we were supported by Dr Abel and clinically by Dr Hugh Young and Dr George Walker Under these happy auspices Dr Geraghty and the author launched the phthalein test

EARLY STUDIES OF DISTURBED FUNCTION IN RENAL DISEASE

The earliest observations on the elimination by the kidney in disease were those of Hahn who noted the absence of the odor of violets in the urine of gouty subjects after the injection of turpentine and of Rayer who noted the absence in nephritis of that peculiar odor which normally is present in the urine after eating asparagus It is probable that the functional tests originated from the study of the faulty excretion of drugs giving rise to evidences of toxicity in certain diseases of the kidney Various investigators (Todd[56] Charcot Roberts[46] Duckworth[5] Chauvet[1]) published accounts of the retardation in the excretion of various drugs among which may be mentioned Dover's powder mercury iodides alkaline carbonates salts of potassium and sodium quinine and salicylic acid In 1877 Bouchard conceived the idea of using fuchsin for estimation of the excretory power of the kidney but little was accomplished until twenty years later when Achard and Castaigne[3] introduced methylene blue into the field and demonstrated the possibility of utilizing dyes in attacking this problem

The work on osmotic pressure by Raoult and Van't Hoff was

applied as *cryoscopy* by Dreser,[13] Korányi,[29] Hamburger,[24] and Leon Bernard in studying the work performed by the kidney The electrical *conductivity* of the urine was studied by Dawson Turner "A blood of high resistance indicates that the proportion of salts in the blood is small or that the proportion of corpuscles present is large Hence a high resistance of the blood but a low *resistance of the urine is indicative of health*" A hemorenal salt index—the ratio of the electrical resistance of the blood and urine was suggested

The *methylene blue* test was introduced in 1897 by Achard and Castaigne [22] The drug could be given by mouth in ¼-gram doses but was usually administered by intramuscular injections, 15 minims of a 5 per cent solution In health the [illegible]

this field

Indigo-carmine was used by Heidenhain[25] in his investigation of the physiology of the kidney He concluded that the epithelial cells of the convoluted tubules were the portions of the kidney substance which excreted the dye In 1903, Voelcker and Joseph proposed the use of the dye for the testing of renal function The test was performed as follows Twenty cc of a 0 4 per cent solution are injected into the muscles of the gluteal region In stronger preparations the indigo-carmine does not remain in solution A sufficient quantity must be used to give a deep color to the urine, the injection causes some pain and local irritation In normal individuals the urine becomes tinged a greenish-blue ten to fifteen minutes after the injection, and subsequently becomes deep greenish-blue when good elimination occurs According to Kapsammer,[27]

toxic and that albuminuria and convulsions had been induced The next week the child died The autopsy revealed a marked chronic interstitial nephritis Fortunately Dr Thayer was present at necropsy and stated that the test had revealed the true nature of the disease and that the clinicians were forced to admit a mistake in diagnosis This incident raised the value of the phthalein test considerably Subsequent pathological studies by Dr Thayer and Dr Roy Snowden helped in attracting to it worldwide attention

The normal or increased secretion of phthalein in certain cases of so called parenchymatous nephritis gave great concern Pepper and Austin [44] and later W Baetjer collected several cases of this type The subsequent recognition of nephrosis as a separate type of renal disease clarified the situation Today we realize that in cases of pure nephrosis the phthalein excretion is not diminished nor do urea and creatinine accumulate in the blood Wilbur has recently reported a series of 32 carefully studied cases from the medical services of the Mayo Clinic in all of which the phthalein output was normal

Geraghty and the author s first publication included over 200 functional tests on 150 subjects which seemed to justify the following conclusions (1) Phenolsulphonephthalein is better adapted for a functional test than other drugs previously employed on account of its early appearance and the rapidity and completeness of its elimination by the kidney (2) The quantitative estimation of the amount of drug excreted is simple and accurate (3) The permeability of the kidney for this drug is decreased in chronic parenchymatous and chronic interstitial nephritis the decrease being most marked in the interstitial variety (4) The test has proven of practical value in revealing the true renal condition in cases with [illegible] than the urinary [illegible] e surgeon [illegible] functional condition (5) The test led to a striking improvement in the treatment of prostatic obstruction indicating those cases which need preliminary treatment before operation (6) In unilateral and bilateral kidney diseases the absolute amount of work done by each kidney as well as the relative proportion can be determined when the urines are obtained separately

The second communication corroborated the earlier conclusions and presented evidence indicating that (1) The absorption of phenolsulphonephthalein from the lumbar muscles is better than from the gluteal while the latter is superior to subcutaneous absorption (2) Administration into the lumbar muscles is the method of choice (3) Experimentally the diuretics which stimulate the renal cells to increased activity cause some increased secretion while those that act mechanically produce no increased secre-

tion clinically diuretics do not influence the phthalein output (4) Experimental evidence seems to indicate that phenolsulphonephthalein is excreted mostly by the tubules but probably also to a slight extent by the glomeruli (5) The renal cells display a striking specificity in the excretion of phenolsulphonephthalein (6) The test is of value from a diagnostic and prognostic standpoint in nephritis revealing the degree of functional derangement in nephritis whether of the acute or chronic variety (7) In the cardiorenal vascular cases the test has proved of value in determining to what degree renal insufficiency is responsible for the clinical picture

During this period Schlayer and Hedinger[53] were attempting functionally to differentiate glomerular and tubular involvement and to classify the nephritides on this basis Schlayer s methods interesting from an academic point of view have added little to the classification of the nephritides Dr Reginald Fitz Geraghty and the author[49] combined the phthalein studies with Schlayer s tests the determination of lactose the salt and water tests and the potassium iodide test They concluded that the functional capacity of the kidney could be determined more accurately through these

of the
value
sub
creted

in cases of pure nephritis in response to sodium chloride stimulation was considered possibly of diagnostic value The potassium iodide test was found of little value The accumulation in the blood of incoagulable nitrogen in cases of nephritis was thought to be of great importance

OTHER FUNCTIONAL TESTS

Urea and Its Determination

in 1890

Great progress came from improvement of methods of study of urea and from Grehant s and later Ambard s studies of the laws of urea excretion (1912) Folin s method for the determination of non protein nitrogen was introduced (1912) and Marshall s urease

method for determining urea (1913) This was followed by a permanent urease preparation by Van Slyke and Cullen which further simplified the urea determination

Thereafter the work followed three main lines all pursued simultaneously (1) Estimation of blood urea and of non protein nitrogen in determining renal function (Marshall Rowntree and collaborators Folin etc) (2) Study of rate of excretion of urea (Ambard McLean Selling Addis and Watanabe Van Slyke and his collaborators) these resulted in Ambard s constant and in McLean s index and Van Slyke s urea clearance test (3) The rate of urea excretion after oral administration by Monakow Addis and Watanabe and McLean The method of choice relative to rate of urea excretion is in all probability the urea clearance test of Van Slyke representing one of the most accurate approaches to the determination of renal function In practice however the *profession at* [illegible] *great extent on the simple deter*mination of

An ingeni [illegible] ation was developed by Hench and Aldrich [6] Recognizing the rather uniform distribution of urea throughout the tissues and body fluids they developed the salivary urea index whereby the urea of the saliva as determined by an extremely simple method indicates roughly the extent of urea retention in the body They also employed the mercury combining capacity of blood or serum as an index of urea retention in the blood

Creatinine, Uric Acid and Sulphate Retention in the Blood — Another important clinical test of renal function the estimation of the blood creatinine was introduced by Folin its clinical value being established largely through the studies of Myers and his collaborators Fine and Lough [37–42] It has proven of unusual value from the standpoint of prognosis in renal disease

of renal injury It has [illegible]

Concentration and Dilution of the Urine in Indicating Renal Function —Finally the urine itself affords a remarkable index of the

functional capacity of the kidney From ancient times the variability of urinary excretion has been noted and discussed Albarran,[6] in 1904, suggested that dilution response of the kidney to large [illegible]

and determined the capacity of the kidney both to concentrate and to dilute They placed their patients under rigid control and [illegible]

dilution studies into general use Addis and Shevky[4] use as a functional test the specific gravity of [illegible]

Concentration and Excretion Coefficients and Renal Function.— The use of mathematical formulas in determining the work done by the kidney permits more accurate statement of experimental findings, especially in relation to urea This idea was introduced by Grehant,[23] brought into prominence by Ambard[7] and into [illegible]

of utilizing the curve of phthalein excretion, rather than the amount excreted for a given period of time was suggested and discussed by Geraghty and the author,[50] in 1910, and that normal curves for phthalein excretion following its intravenous injection were presented in 1912 At that time it was stated[51]* "When intravenous administration is employed *observations for more than one-half hour should not be used,*' the amount of excretion for this time being almost equal to that for two hours following the subcutaneous injection This statement has been overlooked by some advocates of the urea-clearance test The studies of Geraghty and the author, as published indicated the phthalein output for the first one-half hour is 58 per cent and not, as has been intimated in certain studies, 55 per cent for two hours

Shaw[54], of Miami, introduced a method for using the phenolsulphonephthalein test somewhat analogous to the fractional analysis of gastric secretion He [illegible] output at five- to ten-minute [illegible] tion on the curve or rate of [illegible] recovered in a specified peri[illegible]

* Quoted here because it has been so greatly ignored

affords a more accurate functional test especially in prostatic hypertrophy Habein in the Mayo Clinic followed up this idea in a series of cases of enlargement of the prostate and his results concurred with Shaw's conclusions In certain cases here the total output of phthalein is relatively high The fractional determination allows additional information of great value

If these two tests urea clearance and the phthalein output are to be compared it appears desirable to compare the curve or rate of phthalein excretion with the rate of excretion of urea This is perhaps a challenge to those claiming a superior value for the rate of urea excretion over the phthalein test Under any circumstances such a comparison seems highly desirable academically and clinically since the rate of excretion is probably the true index of the functional capacity of the kidney *

CRITICISM OF FUNCTIONAL TESTS

Tests of renal function have been criticized (1) Most frequently because they afford an index of the functional capacity at one particular time only and afford no clue as to the possibility of functional recovery (2) It is said that the kidney does not excrete all substances with the same facility and that data obtained from the study of the elimination of one substance cannot be applied to others (3) The functional test does not indicate whether the kidney is functioning at its normal rate or at or near its maximum (4) In acute and in chronic parenchymatous nephritis functional tests seem to fail or at least give no adequate idea as to the severity of the renal condition (5) Certain tests have been criticized because of the inaccuracy of colorimetric methods

Despite these criticisms functional tests have come into general use and have proved of great importance in the practice of medicine With several excellent tests available more than one test is usually employed in aiming at a decision Repetition of the test gives information about changes in functional capacity both in medical and surgical diseases of the kidney In the Mayo Clinic the phenol sulphonephthalein test is done first If there is any indication or

* Recently since this paper was written a comparison such as is here suggested has been carried out The Fractional Phenolsulphonephthalein Test in Bright's [illegible] d J A Halsted (Am J Med Sc 1933 186 [illegible]33)

suspicion of disturbance of renal function blood-urea determinations are made and, if these are strikingly abnormal, blood creatinine and occasionally blood uric acid are determined

THE RÔLE OF THE PHTHALEIN TEST IN MEDICINE AND SURGERY

The phenolsulphonephthalein test is valuable in diagnosis, prognosis and treatment in both medical and surgical diseases of the kidney On the medical side it is used to determine whether or not the kidney is actually involved in the disease process, in other words to determine whether disease of the kidney itself must be included or excluded It is of importance in determining the nature of the renal lesion when such exists In nephrosis, for instance the phthalein output is usually normal, occasionally increased In late stages with contracted kidney and probably secondary nephritis the output may be considerably reduced In diffuse glomerular nephritis excretion of phthalein is usually diminished and the degree to which it is decreased affords an index to the extent of involvement This is true in both acute and chronic forms, but it must be kept in mind that in acute types the function may vary greatly within a short period of time In focal nephritis, the phthalein output is rarely reduced In the vascular types of nephritis the functional tests have been of unusual value, especially the determination of the phthalein output In benign forms of hypertension, the phthalein output is normal and the urinary prod
form
the
extr
clinical condition In cardiac disease, the state of the myocardium is often reflected in the renal function During compensation the

This is particularly true in relation to digitalis therapy In this connection the phthalein is a better indicator than the blood urea

In certain forms of intoxication the phthalein output has played an important part in determining the involvement of the kidney Thus in mushroom poisoning which was looked upon as a toxic psychosis a low phthalein output suggested renal injury and uremia was unmasked *In high intestinal obstruction, uremia is often* encountered The blood urea is high but the decrease in the output of the phthalein is a more specific index of renal injury. In polycystic kidney the phthalein output may be very low and the blood urea very high for long periods of time In Addison's disease with

failing circulation during the crises and end stages the urea of the blood increases and the phthalein output is decreased This has been regarded as a toxemia of glandular origin but the decreased phthalein output indicates that it is secondary to renal insufficiency due in all probability to deficient renal circulation In eclampsia

the phthalein

is a toxemia

ial functional

ns connection

the total or combined renal function is the chief consideration In addition information concerning the function of the individual kidney is highly desirable and at times essential

In bilateral surgical diseases of the kidney, hypertrophy of the prostate is a common cause Back pressure on the kidney leads to progressive decrease in renal function This is indicated by the *phthalein test but catheterization of the bladder is essential where* urinary retention is present As a rule where urinary retention is marked tests of blood retention are used by preference

In the vast majority of cases the test by ordinary technique is employed Attention has already been called to the superior value of the fractional test in certain cases where the output for the *hour is near or within normal limits In bilateral tuberculosis* of the kidneys pyonephrosis pyelonephritis and multiple abscesses of the kidney the phthalein output indicates the degree of renal insufficiency In hydronephrosis tests of retention afford a preferable index to function

In unilateral diseases of the kidney the function of the individual kidney can be readily determined and on this surgical judgment and decision as to operation is based In determining the function in the individual kidney the phthalein test excels except where difficulty is encountered in locating the ureteral orifice Under such conditions chromocystoscopy is indicated and indigo-carmine is preferable The phthalein test indicates the extent of injury of the diseased kidney and the capacity of the other kidney to carry

termination Where re

diseases *the phthalein*

...ed by the kidney

phthalein test, the level

...st *and Mosenthal's* test

of concentration and dilution Tests of renal function reach their greatest value only when their findings are properly correlated with the history of the patient the physical findings the urinalysis

REFERENCES

4 ACHARD CH AND DELAMERE V 1899 L exploration clinique des fonctions rénales par la glycosurie phloridzique Bull et mém Soc méd d hôp de Paris p 3 9 (April 7)

5 ADDIS T 1925 A clinical classification of Bright s diseases J Am Med Assn 85 163–16

6 ALBARRAN J 1904 Recherches sur le functionnement normal comparé des deux reins Ann d mal d org génito urin 22 81 126

7 AMBARD L 1920 Physiologie normal et pathologique des reins 2d ed Paris Masson et Cie

8 AMBARD L AND BEAUJARD E 1905 La retention chlorurée seche Semaine méd 25 133 136

9 BRIGHT R 1836 Cases and observations illustrative of renal disease accompanied with the secretion of albuminous urine Guy s Hosp Rep 1 358–400

trans by Millard New York

12 CHAUVET CH 1877 Du danger des médicaments actifs dans des cas de lésions rénales Paris Thèse

13 DRESER 189? Ueber Diurese und ihre Beinflussung durch pharmakologische Mittel Arch f exp Path u Pharmakol, 29 303–326

14 DREYFUS 1898 Contribution à l étude de la perméabilité rénale Thèse de Lyon

15 DUCKWORTH D 1867 Observations on the passage of certain substances into the urine in healthy and diseased states of the kidney Saint Bartholomew s Hosp Rep 3 216–227

Arch Int Med 16 33–37

1 GERAGHTY J T AND ROWNTREE L G 1911 The phenolsulphonephthalein test for estimating renal function J Am Med Assn 57 811–816

22 ——— 1913 The value and limitations of functional renal tests J Am Med Assn 61 939–941

23 GREHANT N 1904 M

le dosage de l urée dans le sang

24 HAMBURGER 1900 U

Anwendung von Gefrierpunkt

Med 28 ?9 309

25 HEIDENHAIN R 1883 Hermann s Handbuch der Physiologie 5 318

26 HENCH, P S, AND ALDRICH, M 1922 The concentration of urea in saliva, J Am Med Assn, 79, 1409-1412

27 KAPSAMMER 1903 Ueber Ureterenkatheterismus und funktionelle

31 McLEA

tion of urea

normal excret

32 MARSH

tion of urea,

141-154

Urea, its distribution

-80

n and the significance

ital uranium nephritis,

35 ——— 1915 Renal function as measured by the elimination of fluids, salt and nitrogen, and the specific gravity of the urine, Arch Int Med, 16, 733-774

36 MOSENTHAL, H O, AND HILLER A 1917 The relation of the non protein nitrogen to the urea nitrogen of the blood, J Urol, 1, 75-89

37 MYERS V C AND FINE M S 1914-1915 The non protein nitro

tate of creatine when administered to man, J Biol Chem,

39 ——— 1915 The metabolism of creatine and creatinine X The relationship between creatine and creatinine in autolyzing tissue, J Biol Chem, 21, 583-599

40 ——— 1919 Comparative distribution of urea, creatinine, uric acid and sugar in blood and spinal fluid J Biol Chem, 37, 239-244

41 MYERS, V C, FINE, M S AND LOUGH W G 1916 The significance of the uric acid, urea and creatinine of the blood in nephritis, Arch Int Med, 17, 570-583

42 MYERS, V C, AND LOUGH W G 1915 The creatinine of the blood

se by feeding

al studies of

2, 81-86

des procédés

6d 2 19-78

nal diseases

11 121 141

1910 An experimental and

kidneys by means of phenol

erap, 1 579-661

An experimental and clinical

renal function in health and

52 ROWNTREE L G GERAGHTY J T, AND MARSHALL, E K JR 1914 A study of the comparative value of functional tests in the surgical diseases of the kidney secondary to obstruction in the lo ver urinary tract Surg Gynec

603–612
56 TODD R B 1857 Clinical lectures on certain diseases of the urinary

R R
of the
Clin

58 VON MERING C 1885 Ueber kunstliechen D abetes Centralbl f d med Wissensch 23 531–532

CHAPTER XIV

THE BLOOD UREA CLEARANCE TEST

By ROGER R HANNON, M D

Introduction —Since the earliest observations on Bright's disease there have been many methods devised to estimate the damage to renal function by measuring the urea in the blood and the rate of urea excretion in the urine The blood-urea clearance test of renal function by Møller, McIntosh and Van Slyke was a logical development of the long course of observation, experiment and study by many investigators These authors have described the development
adult
with
known as ' Studies of Urea Excretion ' (see especially Van Slyke *et al*[5]).

Van Slyke defines the term ' clearance" as *the volume of blood cleared of urea per minute corrected for urine volume when the latter is below 2 cc per minute* The clearance is calculated from the observed urea concentration of the blood and urine, B and U, and the urine volume, V, in cubic centimeters per minute by the formulas

$$(1)\ C_m = \frac{UV}{B} \qquad (2)\ C_s = \frac{U}{B}\sqrt{V}$$

The first is known as the *maximum clearance* and is used when *the urine volume is 2 cc per minute and greater, or above* the augmentation limit The second is called the *standard clearance* It expresses, for comparison, the value in terms of a standard constant urine volume output of 1 cc per minute It has been found that below the augmentation limit the volume of blood, the urea content of which is represented in one-minute excretion, is not a constant, but varies, on the average, in proportion to the square root of the urine volume It is practically impossible to fix the urine volume at a definite standard, but, by means of the square root rule of Austin, Stillman and Van Slyke,[1] the urea excretion that would accompany such a standard urine volume can be calculated fro
well as above
illustrated by
McIntosh and
ing portion of

this portion represents expresses the average effect of urine volume changes below the augmentation limit From the studies of Van Slyke *et al*,[5] the mean maximum clearance for a person of average

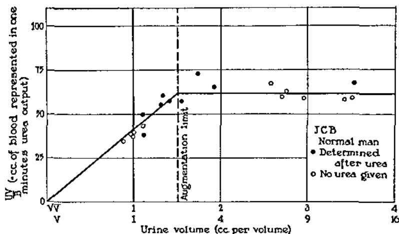


FIG 39 —Urea excretion curve from normal subject

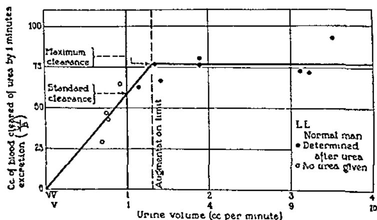


FIG 40 —Urea excretion curve from normal subject

adult size is about 75 cc of blood per minute and the mean normal standard clearance value is about 54 cc of blood cleared of urea per minute If these values are taken as 100 per cent, the per cent of normal renal function can be expressed by the calculations,

$1.33\ C_m$ = per cent normal (from $\frac{C_m}{75} \times 100$), or $1.85\ C_s$ = per cent normal (from $\frac{C_s}{54} \times 100$)

The clearance in percentages of average normal values are therefore calculated as follows

3 Percentage of average normal clearance $= \frac{1.33\ UV}{B}$ when V exceeds 2 cc of urine per minute

4 Percentage of average normal clearance $= \frac{1.85\ U\sqrt{V}}{B}$ when V is less than 2 cc of urine per minute

THE VARIABILITY OF THE BLOOD-UREA CLEARANCE

Studies with this test have shown that in a given individual the probable variation of standard blood urea clearance is ±10 per cent and that the maximum variation is much greater Austin Stillman and Van Slyke[1] have pointed out that this indicates that other factors in addition to blood urea concentration and urine volume affect urea excretion Therefore an erroneous impression would be created by the clearance formulas if they were assumed to express with mathematical exactness the *complete effects of all factors influencing urea excretion* Although the formulas only express the effects of two factors blood urea content and urine volume the limited range of normal variation indicates that they are ordinarily of chief importance in regulating the urea output

It has been found necessary to standardize conditions in nearly all [illegible] red This [illegible] out [illegible] not subjected to any previous routine except that vigorous exercise is avoided and the previous meal should be a moderate one The patient remains quiet while the urine is collected during two succeeding periods of one hour each Inaccuracy in timing of urine collections and the incomplete emptying of the bladder are the chief sources of error A few minutes before the end of the first hour a blood sample is drawn and its urea content is used for the calculation of the clearance for both hours The use of two periods of urine collection serves to diminish the probability of undetected error from incorrect measurement of the collection period and from incomplete emptying of the bladder Errors of either sort reveal themselves by discrepancies between the percentage of normal clearance found for the two periods It has been found desirable to give the subject a glass of water to drink at the beginning of each of the two hours in order to obtain fairly rapid urine flow and thereby minimize the error from incomplete emptying of the bladder

CLINICAL OBSERVATIONS WITH THE CLEARANCE TEST

Comparison of Range and Sensitivity of Test —Under standardized conditions the variation in the clearance values of a normal individual due to other factors than those expressed in the formulas seems to be avoided to as large an extent as is possible The values of 75 cc of blood cleared of urea per minute for the maximum clearance and 54 cc for the standard clearance have been taken as 100 per cent of normal function However this does not mean that the kidneys cannot function at a higher rate of urea excretion or that 100 per cent is the maximum In abnormal or pathological conditions values well above 200 per cent have been observed and this method has been found to be most accurate for estimating hyperfunction of the kidneys Likewise there are conditions in which the kidney function is very low where the phenolsulphonephthalein is excreted in an unmeasurable trace but where the clearance can be measured repeatedly with remarkable accuracy It has been of great interest to follow the course of Bright s disease in this low range where many tests lose their sensitivity Van Slyke *et al*[6] have compared the blood urea clearance with other measures of renal function They have found that the blood urea clearance usually falls below 50 per cent of its normal value before the blood urea content the blood creatinine and the phenolsulphonephthalein excretion show any abnormality Only after the clearance indicates less than 20 per cent of normal renal function are all values for blood urea creatinine content and for phenolsulphonephthalein excretion found outside the limits of normal variations

Acute Hemorrhagic or Glomerular Nephritis Acute hemorrhagic nephritis is marked by the sudden onset of hematuria proteinuria edema and frequently diminished renal function hypertension plasma protein deficit and some anemia During the first weeks of the acute stage it seems impossible to predict the outcome from the severity or mildness of any of these symptoms except plasma protein deficit The renal function may be changed very slightly or it may be almost abolished but it does not appear that we can attach prognostic significance to the degree of early failure nor can we conclude that maintenance of normal renal function during the first months justifies either a good or bad prognosis The author has had patients who during the second and third month after the onset of their illness have had renal function of only 5 to 10 per cent of normal and have shown uremic symptoms but have recovered either completely or to the latent stage Other cases which have at first had but slight impairment of function and few subjective symptoms have shown a gradual loss of clearance progressing to the chronic and eventually to the terminal condition In fact it is the author s impression that cases with insidious onset are

more likely to become chronic than those with a frank acute hemorrhagic onset The interval from onset to attainment of recovery or of improvement to the latent stage in those cases which did not make a complete recovery varied from four to fifteen months These have shown usually by the end of the fourth month improvement in their clearance values which except for an occasional slight setback has been continuous The functional recovery has not always been complete even in some cases where subjective recovery made it impossible to keep the patient in the hospital The author has not had an opportunity to observe many of these latent cases with function of 50 to 60 per cent of normal long enough to ascertain whether the partial functional loss was permanent Later examinations in some cases have shown that the renal function has remained at this lower level for periods of two years others have shown further improvement after their discharge from the hospital It has been of interest that cases which have recovered normal function and have passed through a period of hyperfunction may later have clearance values fixed at the lower limit of normal Exacerbations associated with acute infections have occurred in patients who have had a temporary return of the clearance to normal range and in some instances the disease has taken on a progressive chronic character leading to uremia

In all of the author s cases in which marked fall of the blood urea clearance occurred during the initial months and no definite tendency to rise was noted within four months after the onset progress downward to the active chronic or terminal stage followed In the cases that have recovered or improved to the latent condition the clearance has either remained normal during the initial stage or has begun to rise within four months after onset

The essential for a good prognosis therefore is that within four months after the acute onset the clearance—if it has fallen—will have [illegible]

[illegible] atients who have [illegible] he onset and still have shown no tendency to improve [illegible] function has remained fixed or more often has slowly decreased have been considered as chronic active cases of hemorrhagic nephritis There have been periods of several months or even more than a year when the progress of the disease was arrested There have been periods when subjectively and clinically a patient appeared so improved and felt so well that he has returned to his occupation and active life but the clearance during this time has shown that there was a gradual loss of function This loss in some cases was rapid and in others slow but when it has fallen to 20 per cent or less they have been considered in the terminal stage

Terminal Hemorrhagic Nephritis —With the fall of the clearance

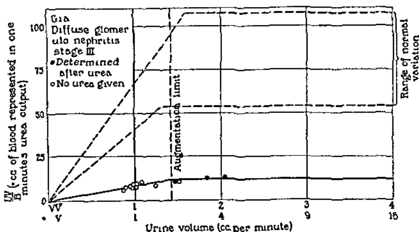


Fig 41 —Urea clearance curve from patient with diffuse glomerulonephritis Stage III

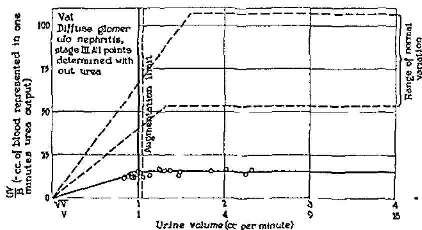


Fig 42 —Urea clearance curve from patient with diffuse glomerulonephritis

retention and a decrease of proteinuria He changes from the 'wet nephritis to the non-edematous, pre-uremic terminal stage The patient rid of the annoyance of the edema, is likely to feel improved and may be able to leave his bed for the first time in months Such

a change is not so obvious in those cases that have a rapid downward course Sometimes edema continues, or nephrotic edema is replaced by cardiac edema After the clearance has fallen permanently below 20 per cent of normal, survival has been less than one year in 60 per cent of the author s cases, one to two years in 30 per cent and over two years in only 10 per cent With the loss of functional elasticity the urea clearance becomes very steady at this time and one can often follow, per cent by per cent the further failure of the urea secreting ability When there remains but 5 per cent of the normal renal function, uremia appears to be inevitable By very careful nursing and dieting, the unpleasant symptoms may still be avoided for a time, but any exertion, shock or indiscretion may bring on uremia and coma

Figures 41 and 42 show the uniformity of the clearance values obtained on 2 patients in the terminal stage These figures also suggest the futility of forcing fluids above the augmentation limit in order to clear the blood more rapidly of urea

Nephrosis or Degenerative Bright's Disease —The author has classified as nephrosis or degenerative Bright s disease those cases which have had an insidious onset, marked edema and proteinuria marked lowering of the plasma proteins without hypertension and without hematuria He has gone most carefully into the history of each patient for evidence of former renal disease history of hematuria, infections etc in order to rule out, if possible, those individuals who are in the latent or chronic active stage of hemorrhagic nephritis with the nephrotic syndrome Careful urine examinations were made microscopically to assure him that the sediment indicated a degenerative rather than an inflammatory lesion The majority of the cases have shown decreased urea clearances Some have shown periods of hyperfunction Two cases have progressed to uremia, urea retention and hypertension At autopsy their kidneys were found to be small and scarred with great destruction of the glomeruli Another case, reported by MacKay and Johnston [2] of sixteen years duration showed very slight lowering of clearance values This patient died with streptococcus peritonitis and the kidneys were the large, pale yellow type usually associated with lipoid nephrosis Even in this case many of the glomeruli were destroyed It appears therefore, that a gradual decrease of urea excreting ability frequently develops during the course of so-called nephrosis and that the disease may end in uremia, the glomeruli then being involved

Arteriosclerotic Bright's Disease —This disease is characterized [illegible] years [illegible] forms [illegible] normal marks the advent of uremic symptoms The fall of the clear-

ance in some cases is gradual over a period of years Other cases may go for a long time with little decrease in clearance, and then show a rapid drop to the uremic level within two or three months At the time of death the more outstanding symptoms may be cardiac, even when the low clearance shows such complete renal failure that a fatal outcome from this cause could not have been long avoided

Summary —Observations carried on during the past ten years lead to the following conclusions

In *chronic* Bright s disease a steady fall in the urea clearance

or sclerotic type

In *acute* Bright s disease on the other hand the clearance may fall to nearly the uremic level and nevertheless recovery may occur Such recovery is rare however unless the clearance begins to rise within four months after the onset

A normal clearance does not necessarily prove the absence of renal disease In cases recovering from the hemorrhagic or degenerative disease the clearance may regain a normal level while one or more other signs such as microscopic hematuria albuminuria or edema persist Such a case cannot be considered to have recovered Usually if the clearance regains normality disappearance of other signs of renal pathology occurs at the same time or later But sometimes complete healing never occurs the disease becomes chronic and the clearance shrinks again This time the shrinkage indicates irreversible destruction of glomeruli

Examples of the progress of the urea clearance in different types of the disease are shown in a monograph covering 66 charted cases [6]

REFERENCES

1 AUSTIN J H STILLMAN E AND VAN SLYKE D D 1921 Factors governing the excretion rate of urea J Biol Chem 46 91 112

2 MACKAY F AND JOHNSTON C 1930 Lipoid nephrosis report of a case of unusual duration Arch Int Med 45 734 741

3 MØLLER, E MCINTOSH J F, AND VAN SLYKE D D 1929 Studies of urea excretion II Relationship between urine volume and the rate of urea excretion by normal adults J Clin Invest 6 427–465

4 ———— 1928 Studies of urea excretion IV Relationship between urine volume and rate of urea excretion by patients with Bright s disease J Clin Invest 6 485–501

5 VAN SLYKE, D D MCINTOSH J F MØLLER, E HANNON R R AND JOHNSTON C 1930 Studies of urea excretion VI Comparison of the blood urea clearance with certain measures of renal function J Clin Invest, 8 357–374

6 VAN SLYKE, D D STILLMAN E MØLLER, E EHRICH W MCINTOSH J F LEITER, L HANNON, R. R., MOORE N S AND JOHNSTON C 1930 Observations on the different types of Bright s disease and on the resultant changes in renal anatomy Medicine 9 257–386

CHAPTER XV

STUDIES IN REHBERG'S CREATININE TEST FOR GLOMERULAR FILTRATION *

By GRACE MEDES PH D AND HILDING BERGLUND, M D
(IN PARTIAL COLLABORATION WITH E BLEGEN M D)

DETAILED STUDIES OF RENAL BEHAVIOR

IN the case of creatinine the direct relation, which generally exists between the concentration of a substance in the plasma and the amount eliminated in the urine is subject to fewer conditions than most urinary constituents This holds not only in comparison with substance like chlorides uric acid phosphates and calcium, for which the conditions governing elimination are admittedly complicated but also in comparison with urea whose elimination has been more extensively studied than any other urinary constituent The important phenomenon justifying this statement is the independence of creatinine excretion and urinary volume It has been possible so to arrange conditions that they permit the use of the creatinine con

difficult or impossible to prove but the reasoning is supported by the facts that creatinine is concentrated more than any other urinary substance (Rehberg) and the excretory ratio $\frac{\text{urine rate}}{}$,

for creatinine higher

amounts to the same,

ion between plasma

lly *even the maximal* value for plasma creatinine is of such a small magnitude that it is inadvisable to base calculations on its variations Since the early work *of Folin the rate of normal* creatinine excretion has been correlated with body weight Eliminating variations in normal plasma creatinine from the calculations, one arrives at the correlation of

* Aided by a grant from the research fund of the Graduate Medical School of the University of Minnesota

normal creatinine excretion with body weight and with the magnitude of glomerular filtration We shall later submit this view to a statistical test

Rehberg[23] found the creatinine excretion to vary roughly with the creatinine content of the plasma, while MacKay[20] so arranged the conditions that he obtained complete proportionality between excretion and plasma concentration The authors present a few examples of reactions given by different individuals For the sake of simplicity they first present the response of a diseased kidney

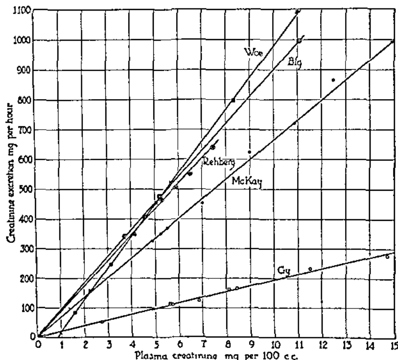


FIG 43 —Ratio of creatinine excretion to plasma creatinine in *Gy* a patient with highly insufficient kidneys and *Woe* and *Blg* two individuals with normal kidneys The curves of McKay and Rehberg have been introduced from their respective data (McKay[20] and Rehberg[1])

Table 15 and curve *Gy* in Fig 43 represent the results of a series of observations on a man, aged twenty-eight years, with primary hypertension The functional capacity of his kidney is reduced 80 per cent or more The plasma creatinine varied from 2 73 mg without any creatinine being given, to 14 7 mg per 100 cc The creatinine excretion in this series of observations

depends upon no other factor than the plasma creatinine concentration. The patient had for weeks been in recumbant position, the blood-pressure remained unusually constant at a high level. The glomerular filtration per minute is independent of the plasma creatinine level and practically constant, varying between 30.7 and 33.5 cc only. This means that the ratio $\frac{\text{excretion (hour)}}{\text{plasma creatinine}}$, as used by MacKay is also constant, varying between 18.4 and 20.1 only. When plotted against plasma creatinine the rate of excretion is expressed by a straight line originating from the zero point. Two

TABLE 15.—MINUTE FILTRATION AND CREATININE EXCRETION AT DIFFERENT LEVELS OF PLASMA CREATININE

SUBJECT Mr G y Aged twenty-eight years Primary hypertension

Creatinine ingested	Time 1931	Plasma creatinine mg per 100 cc		Creatinine excretion mg per hr	Minute filtration cc	Excretion (hour) / plasma creatinine
3 gm	2 21	7.5 8.7	8.1	163.0	33.5	20.1
3 gm	3 6 8 30 A M 10 00 A M	2.75 8.55	5.65	110.7	32.6	19.6
	10 00 A M 1 00 P M	8.55 8.28	8.42	165.9	32.8	19.7
3 gm	1 00 P M 1 30 P M 2 45 P M	8.28 14.70	11.49	231.0	32.6	19.6
	2 45 P M 3 45 P M	14.70 14.70	14.70	276.5	31.2	18.7
	3 7 9 50 A M 11 50 A M	6.84 6.84	6.84	126.1	30.7	18.4
	3 00 P M 4 00 P M	5.70 5.70	5.70	110.0	32.1	19.3
0	3 16 8 00 A M 9 00 A M	2.73 2.73	2.73	50.6	30.8	18.5

facts lend particular significance to these determinations. The determinations constitute three separate experiments covering four days and spread over twenty-four days. During this period there was no noticeable variation in the mode or extent of the renal function in this individual. The second point to call attention to is that the lowest plasma creatinine *determination is 2.7 mg only*, before any creatinine had been given. Even under this condition *the law governing the creatinine excretion* remains unmodified.

At this point it becomes necessary to discuss the significance of the plasma creatinine values obtained when no creatinine has been ingested. Rehberg touches lightly upon this question, avoiding

mination It is worth while to recall the story of the preformed blood creatinine excellently told by Hunter[18] It was found that the so-called preformed creatinine of whole blood reduced picric acid at a different rate from the standard made up from purified creatinine doubt thus being thrown upon the practical specificity of this admittedly unspecific reaction Hunter and Campbell[19] showed that this objection was not valid for the plasma creatinine which they consequently accepted as true creatinine Behre and Benedict[2] on the basis of the irregular behavior of whole blood creatinine toward heat and sodium hydroxide and toward kaolin concluded that preformed creatinine was not present in the blood in appreciable amounts Though no other explanation of the interesting observations of Behre and Benedict seems to have been given their conclusion was disproven by Gaebler and Keltch[11] by the isolation of preformed creatinine from both normal and nephritic blood Though there is little reason to assume that the isolation was quantitative it is important that their isolated material corresponded to about 0 4 mg creatinine per 100 cc normal human blood and in nephritics to about one half of the amount colorimetrically determined In the authors experiment the patient with reduced renal function presented an elevated plasma value for preformed creatinine of 2 7 mg per 100 cc a doubling of the normal value

Referring back to curve *Gy* in Fig 43 or to Table 15 we are impressed with the mathematical precision of the correlation between output and plasma concentration Assuming the value before the ingestion of creatinine as well as all subsequent values to be 1 35 mg too high the curve would move up and reach the zero point for plasma creatinine at an excretion of about 30 mg creatinine per hour This would necessitate the assumption of an active secretion of creatinine Considering the curve where it actually is as the more likely expression of what takes place it is necessary to assume either that both plasma and urine values are correct expressions for the true preformed creatinine or that the other compound or compounds which besides creatinine go to make up the total picric acid reducing plasma content are eliminated [illegible] catinine

medical
results
are atypical but clear-cut The authors have carefully looked into the physical condition of their subject on repeated examinations in the students health service he was found always to have a low blood pressure about 100/60 Observations are made up of six

TABLE 16 —MINUTE FILTRATION AND CREATININE EXCRETION AT DIFFERENT LEVELS OF PLASMA CREATININE

SUBJECT Mr Wee Aged twenty two years Healthy student

Creatinine ingestion	Time	Plasma creatinine mg per 100 cc		Creatinine excret on mg per hr	Minute filtration cc	Excretion (hour) / plasma creat nine
10 gm	10 00 A M					
	11 00 A M	11 07	10 94	1094	167	100 0
	12 00 M	10 08				
	1 00 P M	9 00	8 33	799	160	95 9
	2 00 P M	7 65				
	3 00 P M	6 12	5 70	523	153	91 6
	4 00 P M	5 28				
	4 00 P M	5 28	5 07	457	150	90 1
	5 00 P M	4 86				
	5 00 P M	4 86	4 55	408	149	89 6
	6 00 P M	4 24				
3 gm		3 63	4 13	349	141	84 5
		4 62				
2 gm		3 48	3 13	246	131	78 6
		2 79				
1 gm		2 46	2 27	158	115	70 0
		2 08				
0		1 56		84	90	53 8
Diuresis cc /hr						
0 — 87	9 10 A M	1 38		71	86	51 4
40 gm urea — 96	10 10 A M	1 38		72	87	52 1
528	11 10 A M	1 38		76	91	55 1
240	12 10 P M	1 44		64	74	44 4

different tests, performed on different days, without creatinine and after the ingestion of 1, 2, 3 and 10 gm , respectively The plasma creatinines thus were made to vary from 1 4 to 10 9 mg The $\frac{\text{elimination rate}}{\text{plasma creatinine}}$ presents a straight-line relationship, but the curve reaches the zero point for elimination before the zero point for plasma concentration In other words, the ratio between elimination and plasma concentration is modified by another factor, which we believe to be the filtration rate or volume In this subject it, therefore, appears that the filtration rate is influenced by the plasma-creatinine concentration The glomerular minute filtration rose from 86 to 167 cc , step by step, as the plasma creatinine level rose Table 16 makes clear that this change in minute filtration is not a gradual process as far as time is concerned, the different

of simultaneous

in Fig 43, the
orresponding to

from each plasma creatinine value, moving the curve to the left and starting it from zero, it becomes identical in character with the previous curve, *Gy*, with a constant filtration-rate of 179 cc per

such
what
"cor-

rections The reasons why they consider such a correction unjustified are partly evident from the discussion of the first experiment

10 gm , respectively During the second hour after the ingestion of 2, 3 and 10 gm creatinine, Dr Blegen responded with what under

TABLE 17 —MINUTE FILTRATION AND CREATININE EXCRETION AT DIFFERENT LEVELS OF PLASMA CREATININE

SUBJECT Dr Blegen Aged twenty-eight years

Creatinine ingestion	Time	Plasma creatinine mg per 100 cc		Creatinine excretion mg per hr	Minute filtration
10 gm	6-14				
	7 00 A M				
	9 00 A M	10 34	11 07	996 8	150 0
	10 00 A M	11 80			
	11 00 A M	8 34	8 04	616 0	103 0
	12 00 M	7 74			
	1 00 P M	6 96	6 75	418 0	72 0
	2 00 P M	6 54			
	About for one and a half hours				
	4 30 P M	3 78	3 78	253 0	112 0
	5.30 P M	3 78			
2 gm	6-13	3 09	3 74	340 5	154 7
		4 38			
1 gm	6-11	3 14	2 99	161 3	89 8
		2 83			
0	6-6	1 575		73 0	77 3
0	5-29	1 575		75 2	79 5
0	5-28	1 575		68 6	72 6
3 gm	5-27	5 30	5 21	478 8	153 4
		5 12			

the circumstances appears as his maximum filtration 154 7 cc 153 4 cc and 150 cc minute filtration The corresponding plasma c [illegible] s follows 3 7 mg 5 2 mg [illegible] xcretion rates per hour are f [illegible] plotted against the plasma concentrations are accurately placed upon the straight line *Blg* (Fig 43) originating *from the zero point It shall again be empha sized that each point represents a separate experiment*

Rehberg [7] published a self-experiment the first part of which (Rehberg Fig 43) during four separate determinations showed a *complete proportionality* between rate of elimination and plasma creatinine the straight line laid over the separate points originating from zero The range of the plasma creatinines in this part of Rehberg s experiment was not great 5 3 to 7 45 mg only The range was decidedly greater in MacKay s experiment referred to above (MacKay Fig 43)

Summarizing this part of the experiment it is evident that in *some but apparently not in all subjects under certain conditions* the creatinine excretion is completely proportional to the creatinine concentration of the plasma The curves originating from the zero point in Fig 43 could hardly have been obtained unless the methods for the creatinine determinations in plasma and urine determined essentially or proportionally the same substance or substances in both fluids This conclu ion renders support to the assumption that the normal values for preformed plasma creatinine are essen tially correct

The authors second experiment curve *H ce* showed that even *with a straight line relationship between elimination and plasma* concentration a second factor might influence the elimination namely *the rate of filtration Ordinarily changes in* filtration rate cause a deviation from the straight line relationship (Fig 44) This leads to a discussion of the factors which influence the rate of filtration We have attempted to study the following factors blood pressure rate of blood flow and plasma-creatinine concen tration *The latter we have studied more extensively* than the others In normal individuals high filtration rates were not observed without ingestion of creatinine Repeated tests without creatinine separated by weeks or months but on the same indi vidual have given practically identical rates Patients with incompetent kidneys (Table 15) *frequently show maximum* filtra tion without creatinine ingestion Normal individuals upon inges tion of creatinine show not necessarily a maximum filtration but a high filtration constant from one test to another The minimum amount of creatinine necessary varies A constant filtration rate was not obtained after 1 gm creatinine After 2 gm the results have varied Dr Blegen reached his constant high value after

2 gm, while Dr Mn did not After 3 gm creatinine, the authors obtained the same filtration as after 10 gm Three grams were,

in the ninth hour after the subject had been active in the wards for one to two hours In Dr Mn, after 3 gm, the rate likewise fell in the third or fourth hour These drops in filtration rate are independent of the level of the plasma creatinine

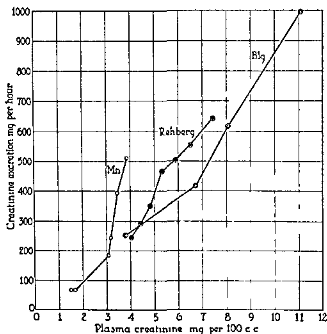


FIG 44 —Ratio between creatinine excretion and plasma creatinine level in *B g* and *Mn* two normal interns showing high ratio immediately following ingestion of creatinine with subsequent variations after different time intervals

STATISTICAL STUDIES IN NORMAL VALUES

Under standard conditions *viz* during the second hour after inges-
berg
113 a
as below normal limits

The authors have determined the minute filtration under the same standard conditions in 60 normal medical students and interns, none of whom showed albumin or pathological sediment in the urine

Wu) ... Wu
The pı ... d for
purity

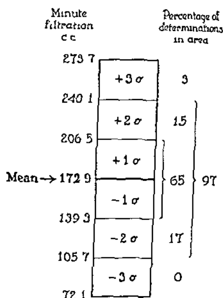


Fig 45 —Minute filtration (creatinine clearance) of 60 normal medical students after ingestion of 3 gm of creatinine showing the range of clearances included in ±1 2 and 3 times the standard deviation together with the percentage of cases in each area

The range of the minute filtration extended from 111 to 253 cc, with a mean value of 172 9 ± 2 9 The standard deviation (σ) was 33 6 ± 1 1 Figure 45 depicts the areas covered by plus or minus one, two and three times the standard deviation, with the percentage of determinations contained in each area Sixty five per cent of all determinations fall within plus or minus once the standard deviation and 97 per cent within plus or minus twice the standard deviation

No definite correlation existed between minute filtration and body weight and no correlation between filtration and plasma creatinine level The basis for the former statement is as follows

The mean weight was 153 35 ± 1 74 pounds, with a standard deviation of 19 93 pounds The coefficient of correlation of weight and filtration was + 0 28 ± 0 12, giving a ratio of the coefficient of correlation to its probable error of 2 34, rendering the coefficient of doubtful significance The mean value of the plasma creatinine was 4 24 ± 0 06 mg The coefficient of correlation of plasma creatinine and filtration was + 0 05 ± 0 12, with a ratio between the two of 0 4

The authors have further determined the minute filtration without previous administration of creatinine in 38 normal students, some of whom had the 3 gm test too The findings are depicted

Minute filtration c c | Percentage of determinations in area

132 0 — +3σ — 2 6
117 5 — +2σ — 15 8
103 1 — +1σ
Mean → 88 6 — −1σ — 63 2 — 94 8
74 1 — −2σ — 15 8
59 7 — −3σ — 2 6
45 2

FIG 46 —Minute filtration (creatinine clearance) of 38 normal medical students without previous creatinine ingestion showing the range of clearances included in ±1 2 and 3 times the standard deviation together with the percentage of cases in each area

in Fig 46 The range of minute filtration lay between 58 and 126 cc with a mean value of 88 6 cc ± 1 6 The standard deviation (σ) was 14 5 ± 0 9 Sixty-three per cent of all values lay within plus and minus once the standard deviation and 94 8 per cent within twice the standard deviation [illegible]

early in this chapter, the twenty-four hours' creatinine excretio

shows a high positive correl
who received no creatinine
relation between weight ar
correlation being + 0 58 ± 0 11 the ratio between coefficient and probable error being 5 45 As already stated no such correlation existed after the ingestion of creatinine

The interpretation of the vastly different filtration rates without and with creatinine must remain tentative It is evident from the earlier discussion that the authors are not inclined to ascribe

one situation but not in the other Little objection should be raised against the interpretation that the filtration rate when no creatinine has been ingested represents all that is needed to meet the excretory demand when no extra load has been imposed and that the higher rate after ingestion of creatinine represents the maximum filtration occurring in immediate response to stimulation of glomerular structures by normal metabolites * The varying filtration rates depicted in Fig 44 demonstrate the almost continuous variations which occur in the course of a day independent of the plasma creatinine level after the first stimulation has worn off Note particularly curve Mn in which the filtration s independence of the plasma creatinine is exemplified!

The authors have attempted to demonstrate the effect of increased blood flow upon the filtration rate In 20 determinations on 18 patients with clinically well-developed hyperthyroidism (Blumgart) the filtration rate after 3 gm creatinine was determined The material included new untreated cases as well as cases of long standing which had been treated with varying degree of success The basal metabolic rates given in Table 18 represent the determinations nearest the day of the creatinine test varying from one day to two weeks The patient with the metabolic rate of −2 a white male is an old case formerly very severe with persisting eye symptoms All patients showed normal urine

The range of minute filtration extended from 111 to 338 cc which is 85 cc wider than in the normal material The patient with the filtration rate of 338 cc was a young man in a very toxic condition untreated presenting a basal metabolic rate of +73 After twenty-one days of Lugol treatment his metabolic rate had dropped to +12 and his filtration rate to 277 cc As shown by

Table 18 15 out of the 20 values fell above the normal mean, 2 values between plus once and twice the standard deviation 3 between +2 and +3 times the standard deviation 1 between +3 and +4 times the standard deviation and 1 beyond +4 times ...

TABLE 18 —FILTRATION RATES IN HYPERTHYROIDISM

Relation to normal mean		Subject	Basal metabolic rate	Plasma creatinine mg per 100 cc	Creatinine excretion mg per hr	Minute filtration cc
$+4\sigma$	5654?	Mr E H	+73	3 17	6?4	337 5
$+3\sigma$		Mr E H	+12	3 35	559	277 3
	97399	Mr F N	+106	4 14	656	264 2
	58744	Mrs M H	+3?	3 34	490	245 3
$+2\sigma$	57070	Mrs S D	+35	3 33	485	?43 4
	51434	Mr C D C	−2	5 43	636	? 1 7
$+1\sigma$	44508	Mrs M H	+5	4 00	516	16 0
	57070	Mrs S H	+36	3 65	390	159 0
	50897	Mr A A	+79	4 14	219	178 5
	5 719	Mrs E H	+38	2 75	10	178 2
	597 06	Miss L T	+36	4 14	442	177 4
		Mrs K H	+33	4 0	4 0	174 6
	59 95	Mr P B	+14	5 46	571	174 3
	50 130	Mrs M J	+	5 75	600	173 7
M	58375	Mrs H L	+4?	3 66	380	17_ 7
	566 4	Mrs S C	+25	5 94	643	166 6
-1σ	49782	Mrs I L	+30	5 67	517	160 1
	5 1309	Mrs F M	+18	5 46	475	129 1
	56897	Mrs G R	+44	5 70	438	125 1
σ	58506	Miss M C	+25	7 08	250	111 2

elevated filtration We present our unselected material * The material further shows one peculiarity not present among the normals viz a significant negative correlation between plasma creatinine and filtration rate the coefficient of correlation being − 0 62 ± 0 1 the ratio between the coefficient and its probable error being 6 5 The plasma creatinines varied between 2 75 and 7 08 mg per 100 cc the mean being 4 51 ± 0 18 There was no significant correlation between plasma creatinine and creatinine excretion the coefficient of correlation being + 0 16 ± 0 16 This fact is surprising remembering that in the experiments recorded

* Our material consists of 13 women and 5 men The mean filtration of six determinations on the men is 235 cc

shows a high positive correl
who received no creatinine
relation between weight ar
correlation being + 0 58 ± 0 11 the ratio between coefficient and probable error being 5 45 As already stated no such correlation existed after the ingestion of creatinine

The interpretation of the vastly different filtration rates without and with creatinine must remain tentative It is evident from the earlier discussion that the authors are not inclined to ascribe

raised against the interpretation that the filtration rate when no creatinine has been ingested represents all that is needed to meet the excretory demand when no extra load has been imposed and that the higher rate after ingestion of creatinine represents the maximum filtration occurring in immediate response to stimulation of glomerular structures by normal metabolites * The varying filtration rates depicted in Fig 44 demonstrate the almost continuous variations which occur in the course of a day independent of the plasma creatinine level after the first stimulation has worn off Note particularly curve *Mn* in which the filtration s independence of the plasma creatinine is exemplified!

The authors have attempted to demonstrate the effect of increased

material included new untreated cases as well as cases of long standing which had been treated with varying degree of success The basal metabolic rates given in Table 18 represent the determinations nearest the day of the creatinine test varying from one day to two weeks The patient with the metabolic rate of −2 a white male is an old case formerly very severe with persisting eye symptoms All patients showed normal urine

The *range of minute filtration* extended from 111 to 338 cc which is 85 cc wider than in the normal material The patient with the filtration rate of 338 cc was a young man in a very toxic *condition untreated presenting* a basal metabolic rate of +73 After twenty one days of Lugol treatment his metabolic rate had dropped to +12 and his filtration rate to 277 cc As shown by

Table 18, 15 out of the 20 values fell above the normal mean, 2 values between plus once and twice the standard deviation, 3 between +2 and +3 times the standard deviation 1 between +3 and +4 times the standard deviation and 1 beyond +4 times

culty to select a group of hyperthyroid cases showing a significantly

TABLE 18 —FILTRATION RATES IN HYPERTHYROIDISM

Relation to normal mean		Subject	Basal metabolic rate	Plasma creatinine mg per 100 cc	Creatinine excretion mg per hr	Minute filtration cc
+4σ	5654[illegible]	Mr E H	+73	3 17	624	337 5
+3σ		Mr E H	+12	3 35	558	277 3
	97399	Mr F N	+106	4 14	656	264 2
	58744	Mrs M H	+3[illegible]	3 33	490	245 3
+2σ	57070	Mrs S D	+35	3 33	485	243 4
	51434	Mr C D C	−2	5 43	630	2[illegible]4 7
+1σ	44508	Mrs M H	+5	4 00	515	1[illegible]0 0
	57070	Mrs S H	+30	3 65	390	189 9
	50827	Mr A A	+29	4 14	219	178 5
	58719	Mrs E H	+38	[illegible] 75	107	178 2
	597706	Miss L T	+36	4 14	412	177 4
		Mrs K H	+33	4 02	470	174 6
	592995	Mr P B	+14	5 46	571	174 3
	562136	Mrs M J	+27	5 75	600	173 7
M	583 5	Mrs H L	+42	3 60	350	172 7
	50624	Mrs S C	+25	5 94	643	166 6
−1σ	48782	Mrs I L	+30	5 67	547	160 1
	5[illegible]1369	Mrs F M	+18	5 46	475	129 1
	5[illegible]6897	Mrs C R	+44	5 70	438	125 1
σ	56506	Miss M C	+25	7 08	[illegible]50	111 2

elevated filtration We present our unselected material * The material further shows one peculiarity not present among the normals viz a significant negative correlation between plasma creatinine and filtration rate, the coefficient of correlation being − 0 62 ± 0 1 the ratio between the coefficient and its probable error being 6 5 The plasma creatinines varied between 2 75 and 7 08 mg per 100 cc the mean being 4 51 ± 0 18 There was no significant correlation between plasma creatinine and creatinine excretion the coefficient of correlation being + 0 16 ± 0 16 This fact is surprising remembering that in the experiments recorded

* Our material consists of 13 women and 5 men The mean filtration of six determinations on the men is 235 cc

in Table 15 and in curve *Gy* of Fig 43 the correlation is complete
An inspection of Table
about as often by low
high plasma creatinine
found in hyperthyroidism *viz the abnormally or unusually high filtration-rates and the frequent independence of plasma creat* inine and creatinine excretion are to be ascribed to increased blood flow alone as we anticipated or whether other factors too have to be considered must be left unanswered As one such factor one might suggest an abnormal relaxation of the glomerular capillaries
Table 19 compares the mean filtrations

TABLE 19 —MEAN GLOMERULAR FILTRATION

Cond t on	No of tests	Mean	Standard de at on (σ)	Coeffic ent of variab l ty
Normal no creat nine	38	88 6 ± 1 6	14 5 ± 1 1	16 3
Normal after 3 gm creat nine	60	17 9 ± ? 9	33 6 ± 2 1	19 4
Hyperthyroidism after 3 gm creatinine	?0	196 0 ± 8 6	55 8 ± 6 0	28 4

OBSERVATIONS ON PATHOLOGICAL KIDNEYS

The basis for the following analysis is 86 separate tests on 82 different individuals the youngest being fourteen years of age the others all being adults All presented some urinary pathology Most types of diffuse renal lesions are represented orthostatic albuminuria is also present No surgical renal conditions have been included The material has been divided into five groups as follows Group I includes 42 tests with filtration rates above *100 cc Group II includes 14 filtration rates from 51 to 100 cc* Group III 13 rates from 21 to 50 cc Group IV 9 rates from 11 to 20 cc and Group V 8 rates below 11 cc The lowest rate was
0 51 cc per mint
per *100 cc blood*
was 292 cc in a
highest was 260 cc in a youth recovering from acute nep
The mean filtration in Group I was 155 cc ± 4 7 the standard deviation was 45 7 cc the mean value being *18 cc less than the* normal mean but the standard deviation 12 cc larger The difference between the means lacks statistical significance The means of the other groups given in Table 20 are dependent on the arbitrarily chosen group limits

The relation between non protein nitrogen and filtration rate will be discussed first This necessitates a review of the limits of normal *non protein nitrogen* Berglund [4] in Folin s laboratory, in 12 young

' ole (laked) blood with 28 Folin and Svedberg[17] in f 31 mg (maximum and minimum 35 and 26 mg, respectively) before breakfast and 31 mg (maximum and minimum 42 and 26 mg respectively) two and a half hours after breakfast The authors possess a series of values from 19 normal individuals physicians and technicians around the laboratory, within the age of twenty two to fifty five years No blood sample was drawn on a fasting stomach The values fall between 23 and 40 mg with a mean of 32 ± 0 7 Our continued experience with fully normal individuals confirms the correctness of these narrow limits for normal non protein nitrogen *

TABLE 20 —SUMMARY OF THE PATHOLOGICAL MATERIAL

Group	No of observations	Mean filtration cc per min	Mean plasma creatinine mg per 100 cc	Mean N P N mg per 100 cc	Diff of means / prob error of diff
Normal 3 gm creatinine	60	172 9 ± 2 9	4 24 ± 0 06	3 0 ± 0 7	
					6 3
Abnormal kidneys I Filtration 101 cc	4?	154 8 ± 4 7	5 2? ± 0 14	39 0 ± 0 8	
					2 8
II Filtration 51 100 cc	14	76 8 ± 2 5	6 65 ± 0 ?9	4? 0 ± 1 ?	
					3 ?
III Filtration ?1–50 cc	13	33 ? ± 1 7	6 ? ± 0 3?	53 9 ± 2 8	
					3 4
IV Filtration 11 ?0 cc	9	17 0 ± 0 4	9 66 ± 0 ?	?1 3 ± 4.2	
					5 2
V Filtration 10 cc	8	5 4 ± 0 7	12 30 ± 1 ?4	16 0 ± 17 0	

T ? of individuals with diseased who possess a filtration rate an non protein nitrogen of 39 mg ± 0 8 which is significantly higher than the normal mean the ratio between the difference of the means and the probable errors of the means being 6 3 There is no definitely significant difference in mean non protein nitrogen between the group with filtration rate above 100 cc. (I) and the group with filtration between

* The variability of normal blood urea was studied by MacKay and MacKay ([illegible]
[illegible]
different from 11 to 39 Compare last paragraph of our discussion and summary

51 and 100 cc [illegible] higher than the norm [illegible] Group III with filtra [illegible] higher than that of Group II Between Group IV with filtration reduced to between 11 and 20 cc and Group III there is a sharp break in the mean non-protein nitrogen, but even in this group which has a filtration not more than 12 per cent, at the highest, of the normal mean, the non protein nitrogen is little more than the double of the normal, 71 as *versus* 32 mg In Group V with a filtration of 10 cc or less the nitrogen retention is marked, but the condition is still compatible with several months of life To summarize, the non-protein nitrogen might show slight elevation above strictly normal values as early as or earlier than impaired function can be demonstrated by change in filtration-rate As functional impairment increases, the non-protein nitrogen shows slight further increase only, until the filtration has become reduced to about 20 cc

The pathological significance of slight elevations of the non-protein nitrogen above normal values has not become generally recognized or accepted, possibly because it occurs also in a variety of conditions in which the kidneys are not primarily involved (Berglund[4]) When the question is confined to a decision between normality or renal damage, any elevation above the normal level has impressed us as significant Folin and Svedberg[17] are of the opinion that with the use of unlaked blood filtrates according to Folin s new method,[10] instead of filtrates of laked whole blood slight elevations of the non-protein nitrogen will prove even more significant Their normal figures two and a half hours after breakfast are minimum 15 and maximum 20 mg, with a mean of 18 mg per 100 cc blood

The plasma creatinine level under uniform conditions after the ingestion of 3 gm creatinine shows a behavior fully parallel with that of the non-protein nitrogen The mean for Group I is slightly higher than the normal mean, the difference being of definite significance, between Groups I to III the differences are slight, while Groups IV and V show rapidly rising values For Groups III to V one might speak of an inverse relation between plasma creatinine and filtration

The filtration, plasma creatinine and non protein nitrogen may all be looked upon mainly as functions of glomerular activity The concentration ratio, $\frac{\text{creatinine (urine)}}{\text{creatinine (plasma)}}$, in contradistinction, may be analyzed as one expression of tubular function No indication exists that the concentrating power has been tested anywhere near its maximum capacity by this ratio The ratio rather expresses the concentration of choice under conditions of compara-

tive freedom The ratio thus might give a different picture of altered function (Table 21) For the first time in this study we here meet with a marked difference in behavior between the normals and the subjects of Group I the median value of the concentration ratio of the latter being only slightly higher than one-half the normal ratio The drop in the ratio is gradual through Groups I to III and differs in this respect from the plasma creatinine and non protein nitrogen but corresponds roughly with the filtration As with non protein nitrogen so even in regard to the concentration ratio the move from Group III to Group IV represents the breaking point of renal function

TABLE 21 —COMPARISON OF THE CONCENTRATION RATIO $\frac{\text{CREATININE (URINE)}}{\text{CREATININE (PLASMA)}}$ OF THE DIFFERENT GROUPS BY QUARTILES

	Min	25 per cent	50 per cent	75 per cent	Max
Normal	15	47	116	180	4 5
Abnormal kidney					
I	15	37	67	131	395
II	15	20	50	108	245
III	5	7	48	54	125
IV	5	6	13	21	35
V	5			15	45

Finally we once more turn to the relation between plasma creatinine and creatinine excretion Direct relation was exemplified in Fig 43 modification or absence of such a relation in Fig 44 in the hyperthyroid material (Table 18) this modification had reached such a degree that only an insignificant correlation existed between plasma creatinine and excretion a high excretion being effected

normal students the coefficient of correlation is $+0.66 \pm 0.05$ (Table 22) Group I of the kidney material includes a number of tests giving a very high filtration the coefficient of correlation is $+0.18 \pm 0.08$ but this difference from the normal coefficient lacks mathematical significance Group II consists of subjects with definite reduction in the mass of filtering renal structures but with a functional capacity more than sufficient for maintenance

309

as

the

normal coefficient and from Group I as indicated by the ratios 6 31 and 6 15 in Table 22 Functionally this indicates that with progressive anatomical destruction the facility of choice in effecting

elimination, as illustrated in Fig 44, and by the hyperthyroid material, is being lost None of the following groups approaches this correlation, though Group III, for instance, includes our subject (*Gy*, Table 15) The coefficients for Groups III to V are of little significance and no discussion is possible

TABLE 22 —COEFFICIENT OF CORRELATION BETWEEN PLASMA CREATININE AND CREATININE EXCRETION

Material	Coefficient of correlation probable error	Diff of coeff / prob error of diff
Normal kidneys	± 0 66 ± 0 05	
		1 89
Abnormal kidneys		
I	± 0 48 ± 0 08	
		6 15*
II	± 0 98 ± 0 01	
		2 75
III	± 0 64 ± 0 12	
		0 76
IV	± 0 46 ± 0 20	
		0 66
V	± 0 25 ± 0 26	

* The ratio between the difference of the coefficients for the normal and for Group II and the probable error of the difference is 6.31

Discussion and Summary —It has been the aim of the authors through the analysis of some 250 determinations of the rate of glomerular filtration clinically, to distinguish the rôle played by two chief mechanisms in renal function glomerular filtration and glomerular blood flow After elimination of glomerular blood flow as a variable the laws of glomerular filtration have been studied Ingestion of creatinine seems to standardize the blood flow, sometimes completely, more often to a lesser and varying degree only Glomerular filtration is passive and physical in nature The reader has opportunity to familiarize himself with the experiments and arguments for and against this assumption The authors further assume that the filtration is identical in health and disease If in health the glomerular filtrate contains as much creatinine as the plasma, there is no reason for assuming that in disease creatinine would come out less easily, since under pathological conditions glomerular permeability is increased rather than decreased, *viz*, protein retained in health, escapes in disease Experimental evidence supports this assumption In Fig 43 the same expression for creatinine excretion holds for the pathological case and for the normals Therefore, when retention is present in nephritis it is due to too little kidney mass through which filtration can take place rather than to altered laws of elimination There is little —tention of urea or creatin- igh the remaining units is As a matter of fact, the

authors have stopped cutting diets below what is needed by the body as a whole even if thereby the filtration of waste products has to take place at a higher blood concentration than when the whole kidney mass is functioning

Given filtration as an essentially constant process with the creatinine concentration of the filtrate directly dependent on its concen

tion in advanced renal disease reduced by anatomical destruction

elimination depend more on the rate of flow than on the plasma concentration of the substance to be eliminated Fig 43 illustrates this situation It is the feature which the authors are particularly desirous of discussing

Without ingestion of creatinine normal individuals show a high positive correlation between filtration rate and body weight In considering this fact it is worth recalling not only that creatinine output is correlated with body weight but also that creatinine output is independent of diuresis that compared with its plasma level the urinary creatinine is concentrated more than any other substance sufficiently investigated and finally that compared with the other commonly studied waste products creatinine is present in the plasma in minute amounts only a characteristic shared with the sulphates In normal individuals without creatinine ingestion it appears as if creatinine determines the rate of glomerular filtration and blood flow

Elevation of the plasma creatinine level alone must lead to increased creatinine elimination even without any increase in the rate of filtration Actually after ingestion of creatinine by normal

correlation between filtration rate and body weight dwindles and becomes doubtful

Instead the authors turn their attention back to the positive correlation between plasma creatinine and creatinine excretion In all curves originating from the zero point in Fig 43 this correlation was unity or complete In the group of normal individuals who had taken creatinine this correlation was less complete The group showed considerable spread of the filtration rates This spread was assumed to be due not so much to individual differences in kidney mass as to different degrees of opening of capillaries For

the high values the play of yet another factor, increased velocity of blood flow, is suggested. For albuminuria, Cloetta did not find this a factor of importance, but we believe that the very high filtration-rates in hyperthyroidism suggest it. Anyhow the filtration rates in hyperthyroidism proved to have such a wide spread that the correlation between plasma creatinine and creatinine excretion disappeared. On the other hand the group of diseased kidneys with normal filtration-rate showed a positive correlation between these factors which correlation did not differ from the

with a function

was practically

referred to *viz.*,

variations in blood flow under the conditions of the test had disappeared as a factor for consideration. From purely diagnostic point of view this fact has been expressed by stating that the creatinine test shows greater regularity in its results in instances *of reduced function than when function is preserved.*

Thus we arrive at the question of the filtration-rate as a test for renal insufficiency. When we join in Rehberg's conclusion, that a decreasing filtration-rate offers an accurate measure of deteriorating renal function we are not fortunate enough to base our conclusion upon comparisons between filtration rates and anatomical studies of diseased kidneys. For such studies Addis and Oliver[1] have set a high standard. It is desirable that the problem also be attacked experimentally by graded surgical reduction of the kidney mass in suitable animals.

The authors' conclusions are based upon the comparison of filtration-rate with the complete clinical picture of the patients studied supplemented by older standardized methods for testing renal function. Their only observations so far warranting a guarded interpretation of reduced filtration-rates are set down in the discussion of Table 75, in Chapter XXX.

The important factor in the discussion so far has been *variation in glomerular blood flow.* *Comparing filtration-rate* with some other features of renal activity the authors are led to a tentative discussion of tubular activity. Even where the filtration-rate was *fully normal their group of pathological kidneys* showed a markedly lower concentration ratio between urinary and plasma creatinine than the normal group and this ratio declined gradually, parallel with the drop in filtration rate, until the latter fell below 20 cc per minute, at which point a sharp further decline in concentration ratio occurred. This point may be considered as the point where renal function seriously breaks down as further shown by the behavior of the non protein ... after creatinine ingestion and of ...

Below this point there is a ...

products

The level of the non protein nitrogen in all the instances in which the renal function is above the breaking point deserves special consideration Against the assumption of the authors that glomerular filtration takes place in the same manner in health and in disease *the fact calls for discussion* that the non protein nitrogen

with reduced function showing no greater elevation than the first Some other mechanism than mechanical retention through reduction of glomerular surface must be operative to cause this elevation The elevation consists chiefly of urea and the authors offer the

plasma level

If this interpretation is worthy of consideration, an inquiry may be made about phenomena that may be interpreted as evidence

in his Mellon lecture[9] brought out the fact that during normal pregnancy urea is present in the blood in much lower concentration than normally The observation has been confirmed by most investigators Among others Judson A Smith working with one of the authors in Folin s laboratory observed values as low as 12 mg non protein nitrogen per 100 cc plasma during the last months of normal pregnancy and values of 14 mg were reported by Hiss[28] while Harding and collaborators[16] on whole blood found the difference barely distinguishable Positive nitrogen balance with low urea production competes with the assumption of decreased backdiffusion as explanation of this interesting phenomenon The latter assumption might be coupled with another one that of decreased tubular reabsorption as explanation of the transient renal glucosuria not uncommonly present during pregnancy

ADDENDA

One of the authors (G M) carried on a series of experiments on

ra

me

dogs Blood flow was measured by the thermo-stromuhr method of Rein[31] since it permits observations to be made without the

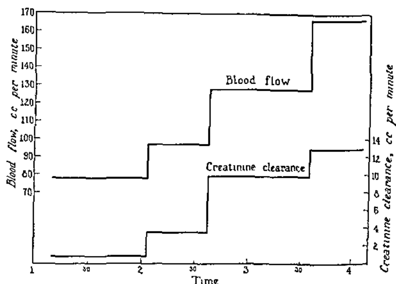


FIG 47 —Parallelism between creatinine clearance and blood flow The changes are typical for the first day of observation (Medes and Herrick Proc Soc Exper Biol and Med)

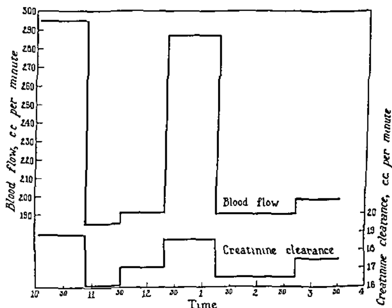


FIG 48 —Parallelism between creatinine clearance and blood flow The second day of an experiment The increase between 12 00 and 1 00 follows a period of exercise (Medes and Herrick Proc Soc Exper Biol and Med)

and observations were commenced Glomerular filtration was measured by Rehberg's method $1\frac{1}{2}$ to 2 gm of creatinine having been injected intravenously about one hour previously All urine was obtained by catheter the bladder washed repeatedly with physiological salt solution and creatinine determined in the combined urine and washings

Medes and Herrick found that where fluctuations were small

was no direct proportionality though in all cases a general parallelism existed between these two factors Table 23 and Figs 47 and 48 give some of their findings

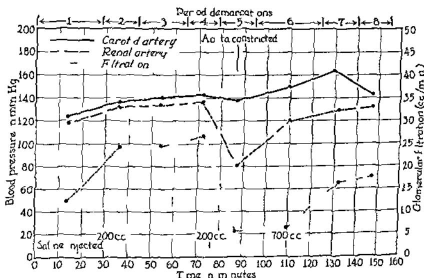


Fig 49 Simultaneous measurements of carotid blood pressure renal blood pressure and creatinine clearance with the blood flow to the kidneys unrestricted and restricted (*Am J Physiol* 107 298 1933)

Blood pressure —Medes and Bellis[24] conducted simultaneous measurements of blood pressure and glomerular filtration in 2 dogs each over a period of several hours The blood pressure was measured simultaneously from the carotid and renal arteries while a loose ligature around the aorta just above the branching of the renal arteries allowed constriction of the artery at intervals during the experiment with consequent lowering of renal blood pressure Urine was obtained from the cannulated ureter of the opposite side and blood for creatinine estimation from the femoral artery

The authors found that the blood pressure in the unconstricted renal artery was invariably lower than that in the carotid the difference averaging about 14 mm Hg Here again was observed a general parallelism between the two processes studied though not a strict proportionality The authors called attention to the immediate response of the kidney to variations of pressure and pointed out that this delicate adjustment supports the hypothesis that creatinine clearance is accomplished by filtration as Rehberg postulates rather than by tubular secretion

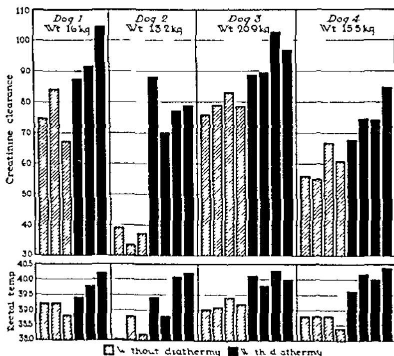


Fig 50 Creatinine clearances of dogs before and during diathermy showing increased filtrations during elevated rectal temperatures

Body Temperature —Grant and Medes[15] *studied the relation* between glomerular filtration and body temperature in a series of dogs before and during diathermy and compared these results with the changes in creatinine clearance-rates in patients with fever and after re

elevation of

with fevers

marked In one instance, for example, three tests with diathermy

were made on one dog, with increases in rectal temperature of 0 3°, 0 7° and 1 1° C respectively, while the corresponding filtrations increased 8 8 13 1 and 25 6 cc per minute Fig 50 gives the results obtained in 29 tests with 4 dogs

Body Weight —Grant and Medes estimated the glomerular filtration per kilo body weight of the dogs used in their experiments and found a value of 3 9 cc per minute The rectal temperatures of their dogs averaged 38 8° C (range, 38° to 39 4° C) They compared this filtration value with the corresponding value found in patients with fevers of infectious origin (average temperature 38 7° C range 37 8° to 40 5° C) The glomerular filtration rates of the non nephritic patients in this series averaged 3 2 cc per kilo per minute The corresponding clearances in Medes and Herrick s series of 25 tests on 7 unilaterally nephrectomized dogs averaged 3 2 cc per kg body weight

References

1 Addis Th, and Oliver J 1931 The Renal Lesion in Bright s Disease New York Paul B Hoeber

2 Behre J A and Benedict S R 1922 Studies in creatine and creatinine metabolism IV On the question of the occurrence of creatinine and creatine in blood J Biol Chem 52 11–33

6 Cushny A R 1926 The Secretion of Urine London Longmans Green & Co

7 Dunn H I 1929 Application of statistical methods in physiology Physiol Rev 9 275–398

8 Folin, O 1905 Laws governing the chemical composition of urine Am J Physiol 13 66–115

9 ——— 1917 Recent biochemical investigations on blood and urine etc Third Mellon Lecture Univ of Pittsburgh

10 ——— 1930 Unlaked blood as a basis for blood analysis J Biol Chem 86 173–178

of blood analysis J Biol

Studies on blood creatinine

1933 Creatinine clearance Clin and Lab Med 1935

16 Harding V J Allin K D and Van Wyck H B 1924 Non pro ... pregnancy J Obst and Gynec

tudier over pathologisk ... Bibliothek for Laeger 74 479–518 538–565

18 HUNTER A 1928 Creatine and Creatinine London Longmans, Green & Co

[illegible]

function al str

[illegible] les C[illegible] mental [illegible] einigen Bemerk [illegible] n Med Nr 15

[illegible]

31 REIS HERMANN 1928 Die Thermo-Stromuhr Ein Verfahren zur fortlaufenden Messung der mittleren absoluten Durchflussmengen in uneröffneten Gefässen in situ Ztschr f Biol 87 [illegible]-418

CHAPTER XVI

RENAL INSUFFICIENCY

BY FRANZ VOLHARD, M D

Introduction —There are few departments of internal medicine in which there has occurred such a change in our viewpoint during the last twenty years alone with such a deepening of our knowledge, incomplete though it still is, as in the field of kidney diseases The progress proceeds, as in many other departments of medicine, from a change in perspective the descriptive consideration of pathological anatomy, which was dominated overwhelmingly by Virchow, has become a dead issue Two new lines of thought have developed First, the question of the cause of the morphological changes, that is, the disease producing process, its pathogenesis This involves consideration not only of the static factor of the anatomical and histological picture, but also of the dynamic factor

this new viewpoint has become dominant

The first of these two more recent considerations that of the pathogenesis of the pathological lesion, has aided the understanding of the various kinds of kidney diseases and has provided the foundation of their newer classification The second, the functional consideration, culminates in the problem of renal insufficiency and

the labyrinth of the pathological physiology and symptomatology of renal diseases and provides fundamental orientation for understanding their general problems, as well as for exercising judgment in special cases

The conception of renal insufficiency is still young It was first formulated by Baron von Korányi[4] at the beginning of this

a consequent tendency for increase in the osmotic pressure of the blood He looked upon the function of the kidney as the maintenance of this pressure at constant level His methods of testing

serum proteins

Physico-chemical Tests of Renal Insufficiency—The most important results of von Korányi's work are the establishment (1) that in renal insufficiency the variability of the secretion of urine is lost (2) that the molecular concentration of the urine as measured by the freezing point test (cryoscopy) diminishes and approaches that of the blood and finally (3) that the molecular concentration of the blood rises by accumulation of non-electrolytes (as measured by conductivity tests) von Korányi also saw that accumulation of electrolytes could be compensated for by retention of water (as measured by the refractometric test) The practical value of this doctrine was meager since it was built up through a study of edematous patients and the great importance of extrarenal factors in the origin of edema and in the composition of the urine was still unknown to Baron von Korányi

Further progress followed along two lines (1) Through chemical studies of the retention of nitrogenous waste products a field opened up by Strauss (2) through studies in the ability of the kidney to vary the composition of the urine—by forcing the kidney and establishing the maximum capacity by the concentration and dilution test The author has employed this test systematically for more than twenty-five years In it the simple determination of specific gravity has been substituted for the determination of

were considered unsuit

he maximum of its con-

are only on observing

the water balance during twenty-four hours or following the ingestion of only 600 to 750 cc of water In the author's test the kidney is forced to its maximum activity both as to dilution through the ingestion of 1500 cc of water and as to concentration through dry diet continued long enough to ascertain maximum concentration The objection that his requirement of 1500 cc of water is unnatural is untenable Maximal activity is always unnatural

The author has confirmed the important statement of von Korányi that the concentration of the urine now measured by its specific gravity approaches in renal insufficiency the specific gravity of the deproteinized blood He found this specific gravity to be about 1010 and called the fixation of the specific gravity of the urine at the level of that of the blood isosthenuria In agreement with von Korányi's terms hypersthenuria and hyposthenuria one could also introduce the term asthenuria indicating absolute loss of concentrating ability

Along with loss of concentrating power the ability of the kidney to excrete a urine of large volume and low specific gravity also disappears The author is not sure whether this loss of diluting power is a renal factor or whether it is dependent upon the high degree of retention of solid substances in the blood In other words if it were possible to reduce the urinary constituents retained in the blood to a normal level by some other method might not the kidney be able to put out a dilute urine?

The systematic application of these principles to the study of the functional capacity of the kidney has rendered the greatest service in the understanding of renal diseases and their symptoms and in their classification and separation into stages and clinical

for testing kidney function have been brought forward Individual *foreign or naturally occurring substances have been deter*mined quantitatively in the urine and their elimination compared with the output of a normal kidney during the same period The observation that many edematous patients whose salt elimination is greatly diminished present a normal excretion of the nitrogenous urinary const [illegible]
was found le [illegible]
functions of [illegible]
many *years different renal syndromes have been designated as azo*temic (nitrogen retaining) and chloremic (chloride retaining)

It must be recalled in consideration of the first of these two groups the azotemic even in those cases in which nitrogen retention is

blood When complete los [illegible]
chloride content of the urine will still be many times as great as that of the nitrogen in proportion to its higher concentration in the plasma *i e when chlorides are present to the amount of* 600 mg per 100 cc [illegible]
blood is 50 mg per [illegible]
urine to the amoun [illegible]
urine

In the second group of patients with poor salt and good nitrogen elimination the so-called chloremic type the author was able to demonstrate that the impairment in this case does not lie in the kidney but in the periphery it consists not in a decreased permeability of the renal elements but in an increased permeability of the peripheral capillaries *Such an insufficiency may* therefore

l the spongy subcutane-
a Vorniere Balance
value because they do
not differentiate between renal and extrarenal factors influencing rate of output and there is scarcely one method free from such sources of error For example in the urea-concentration test introduced by Maclean and de Wesselow a kidney is considered impaired if 2 per cent concentration of urinary urea is not reached two hours after ingestion of 15 gm of urea However a polyuria induced by mobilization and elimination of edema fluid may simulate impaired renal function

Tests With Dyes —Least disturbed by extrarenal factors are perhaps the dye tests the indigo-carmine test of Voelcker and the phenolsulphonephthalein test introduced by Rowntree and Geraghty But it appears for example that excretion of indigo-carmine by one healthy kidney may be severely impaired by some reflex action or toxic substance from the diseased opposite kidney and may be found normal after surgical removal of the diseased organ

The phenolsulphonephthalein test particularly popular in the United States is influenced by cardiac decompensation Slight impairment of the renal function is difficult to judge with certainty Researches of Marshall and Vickers as well as of Schlayer and his school have even demonstrated the surprising fact that the dye-stuffs themselves pass from the blood into the tissues before they *make their way into the urine so that no conclusion may be drawn* as to the amount circulating in the blood and its proportional delivery to the kidneys These observations seem to offer an argument against the idea so widespread that in the glomeruli simply a protein free filtrate is produced

Tests Based on the Excretion of Nitrogenous Waste Products —Among the chemical methods which have made it possible to demonstrate the retention of metabolites the determination of the non protein nitrogen first extensively used by Strauss [7] has well retained its place The same holds true for the convenient though less accurate hypobromite method for urea Numerous factors besides true kidney disease influence the level of the blood urea and the non protein nitrogen such as cardiac decompensation probably through the slowing of the renal circulation and oliguria fever infections surgical interventions acting by overdestruction of body protein After enormous losses of water and salt by vomiting or diarrhea (cholera paratyphoid) we have observed values for the non protein nitrogen as high as 200 to 300 mg per 100 cc values otherwise found only in true uremia

No complete parallelism exists between the height of the blood urea and the degree of kidney insufficiency For instance with

moderately advanced kidney insufficiency *the level of the blood* urea though elevated will vary with the protein intake a high intake will raise the level and a low reduce it more than would normally be the case A kidney with impaired function may maintain the body for a long time in nitrogen equilibrium though by means of an elevated blood urea level With this knowledge we reach the important rule that urea excretion depends upon the urea concentration in the blood—in contradistinction to what holds for the excretion of dyes and probably also for chlorides

Ambard[1] attempted to devise for urea and later for other sub stances also a mathematical expression for the relationship between concentration in the blood and excretion The pith of Ambard s rule is The ratio of the concentration of urea in the blood to the square root of the urea output in twenty four hours is constant *and in the normal individuals equals 0 07 It may be written* $\frac{Ur}{\sqrt{D}} = k = 0\ 07$ where Ur stands for grams of urea in 1000 cc of blood and D represents grams of urea excreted per twenty four hours

What is the meaning of this constant? If the relationship $\frac{Ur}{\sqrt{D}}$ is constant then for every case we can calculate the corrected blood urea value Ur_x which would be needed to maintain the normal *excretion of urea* D_n

$$\text{Since } \frac{Ur}{\sqrt{D}} = \frac{Ur_x}{\sqrt{D_n}} = k$$

$$\text{then } Ur_x = k\sqrt{D_n}$$

If [illegible]
four [illegible]
Ur_x [illegible] g
the constant $\frac{Ur}{\sqrt{D}}$ by 5

The use of this may be illustrated with the following examples If a subject has a blood urea value expressed in grams per 1000 cc *of 0 28 and an output of 16 gm urea per twenty four hours* we may show that his output corresponds to an excretion of 25 gm in twenty four hours with a normal *blood urea value of 0 35 gm* *i e* since $\frac{0\ 28}{\sqrt{16}} = \frac{Ur_x}{\sqrt{25}}$ $Ur_x = 0\ 35$ gm But if his output with a blood urea value of 0 40 gm should amount to only 16 gm per twenty four hours then $\frac{0\ 40}{\sqrt{16}} = \frac{Ur_x}{\sqrt{25}}$ *and* $Ur_x = 0\ 50$ *gm* which is to say in order to excrete a normal amount of urea his blood urea would have to be at the level of 0 50 gm per liter of blood or 50 mg

per 100 cc Again with a urea value of 0 60 gm and a urea output of only 16 gm per twenty four hours Ur_x would equal 0 75, that is, it would have to be 75 mg per 100 cc, in order to produce a normal output of 25 gm urea in twenty four hours

If with this same blood urea level of 0 60 gm per liter his excretion fell to 9 gm per twenty four hours Ambard s constant would be $\frac{0\ 60}{\sqrt{9}} = 0\ 20$ and the blood urea value needed for a normal excretion would be $\frac{0\ 60}{\sqrt{9}} \times \sqrt{25} = 1\ 00$ gm per liter, or 100 mg per 100 cc Thus by multiplication of Ambard s constant by 5 in any given case a clear picture of the degree and significance of the existing azotemia (nitrogen retention) can be obtained

Ambard also used the constant (k) to compute the amount of functioning kidney in pathological cases He stated that the constant of a pathological kidney is related to that of the normal one inversely as the square roots of their functioning masses ... a constant of 0 11 ... the normal con

In Ambard s work we had therefore won a real measure of kidney insufficiency i e of the loss of kidney parenchyma in percentage presuming that the relation given by Ambard is really a constant The author cannot here enter into a criticism of Ambard s constant nor of the various modifications of it He can only mention the excellent experiments of Addis and Drury and of Van Slyke and his co-workers who have evolved a somewhat different relationship between the blood urea values and the urea output Addis and Drury and others have found that the rate of urea excretion is *proportional simply to the concentration of urea in the blood* and not to the square of the concentration as Ambard believed Van Slyke and co-workers whose method described elsewhere in detail (p 210) probably offers at present the best substitute for Ambard s added important new modifications But it must be remembered that all chemical methods including Ambard s are tests merely for separate physiological processes and cannot reveal the functional capacity of the organ as a whole

Concentration and Dilution Tests of Volhard —The one method which gives an estimate of the total functional capacity of the kidney seems to the author to be the simple dilution and concentration test because in addition to offering a measure of capacity, it also reveals the manner of working of the insufficient kidney With the dilution test we determine the maximum activity of one chief constituent of the kidney the glomeruli and with the concentration test we measure the maximum capacity of the other chief

constituent the tubules. Normally these structures differentiated for different functions are grossly independent of each other, that is to say, with normal tubular activity large amounts of solids might be excreted with small loss of water, while with diminished concentrating power more water must be used for the elimination of the same amount of solids. An interdependence replaces the former independence. In such a case the concentration test tells us how far tubular function—concentration—is impaired; the dilution test tells us of how great a polyuria the kidney is capable, that is, how far polyuria can compensate for loss of concentrating power.

The Insufficient Kidney. Pathological Physiology.—It is a great mistake to believe that the known polyuria of contracted kidneys denotes healthy capacity for secretion of water. Given an individual with a polyuria of 4 liters in twenty-four hours, these 4 liters may represent his total capacity to excrete water, whereas the normal healthy kidney is able to put out 12 to 24 liters in the same time or 500 to 1000 cc. in one-half hour.

That this compensatory polyuria has nothing to do with hypertension is unquestionable. It is quite independent of blood pressure. Also it is not the result of a primary polydipsia. It is a compulsory polyuria, a *Zwangs* polyuria, which continues during the concentration test with dry foods, mobilizing tissue fluids so that body weight may decrease by several kilos until progressive loss of water forces us to give up the concentration test and let the thirsty tissues drink.

If the demands for excretion of solids are decreased through restricting the salt and nitrogen intake, the compulsory polyuria disappears, thereby revealing its compensatory character.

This picture of renal insufficiency, going on from hyposthenuria with compensatory polyuria to isosthenuria with pseudo-normal urine and eventually oliguria, is the same whether the result of nephritis, sclerosis, amyloidosis or polycystic degeneration of the kidney. It is of theoretical and practical importance that the same picture is produced if the tubules are injured by pressure, for example, by retention of urine in the bladder due to prostatic hypertrophy, phimosis, detrusor paresis, etc. In these cases, in which the urine is usually free from albumin and nothing points to a kidney disease, the patient complains of an unexplained thirst with dry mucous membranes, hoarse voice, bad taste in the mouth and loss of appetite.

The symptoms of renal insufficiency are often overshadowed by stomach complaints. The glomeruli remain well preserved for a long time; the polyuria is pronounced and may after sudden release of the retention become very abundant and reach a degree dangerous to life. With proper handling the concentration power may return to normal. The necessity of emptying the distended bladder very gradually is not sufficiently appreciated; without such precaution anuria might develop and death follow.

What is the significance of the phenomenon of isosthenuria? Is it an expression of the function of the diseased kidney elements an osmotic asthenia of the diseased kidney, as von Korányi believed? This appears improbable, because if in animal experiments the total kidney mass is reduced to one-fourth through single nephrectomy and partial resection of the remaining kidney, as has been done by Bradford and Allen isosthenuria will result In the author's experiments the same results followed upon single nephrectomy and ligation of two out of three of the branches of the artery to the remaining kidney (Mark) He therefore looks upon what happens in renal insufficiency as the diuresis of a quantitatively reduced kidney that is it is not the diuresis of the diseased structures, but of the still healthy elements provided their number has been reduced below a certain limit

Histology —The histological picture of kidney insufficiency, whether produced through subacute or severe chronic nephritis

whether the patient died from renal insufficiency or not If so, the kidney resembles an indurated lung with vicarious emphysema Islands of dilated tubules appear like air filled blisters in a sea of

bound up with capacity for storage condensation and absorption of urinary constituents in the highly developed structures of the tubules The cubical shape and abundant protoplasm of the tubular epithelium are important characteristics If this epithelium

deformation of the epithelium we conceive to be a condition of exhaustion The cells always at work are not given time for recovery and rebuilding of the protoplasm while normally intervals of work and rest alternate and changes of shift exist between resting and working periods With the structural change goes an alteration in physico-chemical qualities The normal epithelium with its abundance of protoplasm acts as a high wall and is able to preserve an osmotic pressure within the lumen widely different from that outside The endothelial-shaped cells do not possess this power An equalizing of the osmotic pressure takes place but without equalization of the partial concentrations A urine isotonic with the blood results

Other Urinary Changes —Another peculiarity of the urine in renal insufficiency so deserving of attention is its pale watery appearance or lack of typical urinary color As shown by the author's co worker Becher[3] this paleness is due not to retention of the urochrome the plasma too being paler than normal plasma but to a failure on the part of the kidney to oxidize the colorless urochromogen That unoxidized chromogen is present in the pale urine was demonstrated by Becher by shaking the urine with ka lin or by exposing it to ultra violet light normal urinary color develops This simple procedure may well be included among the tests for renal insufficiency

How can we estimate the prognosis in renal insufficiency? Here also the investigations of Becher have made important contribution He found that the degree of urea retention in the blood does not give a correct indication of the danger One may even say that the accumulation of urea in the blood is not dangerous as the blood urea concentration may be elevated even more by ingestion of urea without risk Becher was able to show that the symptoms of true uremia parallel the accumulation of products of intestinal putrefaction as phenol phenol derivatives paracresol and aromatic oxyacids in the blood A discussion of the part played by the accumulation of these substances in the development of uremic symptoms and the modification of the xanthoprotein test which Becher devised for them are given in Chapter XXXIX on Uremia

Value of the Conception of Renal Insufficiency —The more accurate knowledge of renal insufficiency is not only of practical

the
ncy
ub

acute course if the disease passes directly from the acute stage into a stage of insufficiency of a subchronic course if this stage is reached in a few years and of a chronic course when there are many years or decades before insufficiency develops

exception to be consequences of renal insufficiency Questioning whether each phenomenon individually occurs only with or also without renal insufficiency the author has come to the surprising conclusion that neither edema nor hypertension nor retinitis nor eclamptic uremia can be considered the result of kidney insufficiency Thus the way becomes free for the investigation of the pathogenesis

of these important and interesting effects of kidney disease, each one of which presents a problem of greatest complexity.

Summary.—Kidney insufficiency is a quantitative problem; it *results from a reduction in the number of functioning renal units*, a reduction which ultimately brings about a qualitative change in its manner of working, in that it is forced to work continuously at maximum capacity

This is shown by a decrease in concentrating ability, hyposthenuria, with a compensatory *Zwangs*-polyuria advancing to a total loss of concentrating ability, isosthenuria The isosthenuric urine is of constant quality and concentration, produced as it is by a kidney characterized by an inadequate number of renal elements and working night and day

The total concentration of this urine equals that of the deproteinized blood and is represented by the specific gravity of 1010.

The partial concentrations in urine and blood may be quite different

The total concentration of blood and urine becomes the same because the normally cubic tubular epithelium with abundant protoplasm becomes transformed through exhaustion to thin membranes

The criterion of the degree of kidney insufficiency is the concentration test

The criterion of the capacity for compensatory polyuria (the prognosis) is the dilution test

The criterion for judging the danger to life, the xanthoprotein test

References.

1 Ambard, L 1910 Le taux de l'urée dans le sang et l'élimination de l'urée dans l'urine, Compt rend Soc d biol, 69, Part 2, 411 and 506

2 — 1920 Physiologie normale et pathologique des reins, 2d ed, [illegible]

[illegible]

Thieme, 2, 133 190

5 Kovesi, G, and Roth-Schultz, W 1904 Niereninsuffizienz bei Nephritiden, Leipzig

6 Lublin, A 1921 Die Ambardische Harnstoffkonstante, Biochem Ztschr, 125 187

7 Strauss, H 1902 [illegible]

8 Volhard, Franz [illegible] Schrumpfnieren, Verhand[illegible]

9 — 1918 [illegible] Berlin Julius Springer

10 — 1931 II Auflage, vol 1

Other Urinary Changes —Another peculiarity of the urine in renal insufficiency so deserving of attention is its pale watery appearance r la k of typical urinary color As shown by the author s co-worke Becher [8] this paleness is due not to retention of the urochrome tl e plasma too being paler than normal plasma but to i f lu n the part of the kidney to oxidize the colorless urochromogen That unoxidized chromogen is present in the pale u t s lemonstrated by Becher by shaking the urine with l n r l exposing it to ultra violet light normal urinary color l elop Il is simple procedure may well be included among the ts for en l insufficiency

I n we estimate the prognosis in renal insufficiency? Here

ol l urea concentration may be elevated even more by ingestion of urea witl out risk Becher was able to show that the symptoms of true uremia parallel the accumulation of products of intestinal putrefaction as phenol phenol derivatives paracresol and aromatic oxy acids in the blood A discussion of the part played by the accumulation of these substances in the development of uremic symptoms and the modification of the xanthoprotein test which Becher devised for them are given in Chapter XXXIX on Uremia

Value of the Conception of Renal Insufficiency —The more accurate knowledge of renal insufficiency is not only of practical but also of theoretical significance It is of practical importance in that we are better able to separate the individual case into stage and clinical course Thus it has become practical in diffuse glomerul

cases

an l b

acute

a stage of insufficiency of a subchronic course if this stage is reached in a few years and of a chronic course when there are many years or deca les before insufficiency develops

The theoretical significance is as follows Formerly all the manifestations of kidney diseases such as dropsy increased blood pressure retinitis albuminurica and uremia were considered without exception to l e consequences of renal insufficiency Questioning whether each phenomenon individually occurs only with or also without renal insufficiency the author has come to the surprising conclusion that neither edema nor hypertension nor retinitis nor eclamptic uremia can be consi lered the result of kidney insufficiency Thus the way becomes free for the investigation of the pathogenesis

'isease, each

problem, it
ts from a reduction in the number of functioning renal units, luction which ultimately brings about a qualitative change in anner of working in that it is forced to work continuously at mum capacity

ns is shown by a decrease in concentrating ability, hyposthenuria, a compensatory *Zwangs*-polyuria advancing to a total loss of entrating ability, isosthenuria The isosthenuric urine is of con- quality and concentration produced as it is by a kidney acterized by an inadequate number of renal elements and ing night and day

rent

ne total concentration of blood and urine becomes the same use the normally cubic tubular epithelium with abundant oplasm becomes transformed through exhaustion to thin mem- es

ne criterion of the degree of kidney insufficiency is the concen- on test

ne criterion of the capacity for compensatory polyuria (the nosis) is the dilution test

ne criterion for judging the danger to life, the xanthoprotein test

REFERENCES.

AMBARD L 1910 Le taux de l'urée dans le sang et l'élimination de dans l'urine Compt rend Soc d biol 69 Part 2 411 and 506
— — 1920 Physiologie normale et pathologique des reins, 2d ed, Masson et Cie
BECHER E
nkranken
VON KORÁNYI
te in ihrer
ol gisch e C
ne 2 133 1930
KOVESI K, AND ROTH-SCHULTZ W 1904 Niereninsuffizienz bei ritt len Leipzig
LUBLIN A 1921 Die Ambardsche Harnstoffkonstante Biochem r 125 187
STRAUSS H 1902
VOLHARD FRANZ
in pflieren Verhan
— — 1918
n Julius Springer
— 1931 II Auflage vol I

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O BURR PH D AND GRACE MEDES PH D

DIETARY FACTORS IN FORMATION OF URINARY CALCULI

JOLY in a review of etiological factors in stone formation states that there is no very conclusive evidence that race or heredity is important A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine Beyond this climate seems to be relatively unimportant In regard to geographical distribution he concludes All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India Mesopotamia and South China) are districts where

and dietary

Vitamin Deficiency of Diet A considerable amount of experi

out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time In a later summary of their work Mendel[33] stated that they found many more cases among their rats on a diet deficient *in vitamin A * and stated that when it is recalled that phosphatic* calculi deposited in neutral or alkaline urine which in turn frequently owes its reaction to bacterial decomposition are found extensively among peoples living example in the tropics and Far East on diets quite unlike t regime of most Americans and Europe ssible relat calculi to dietary factors is at once pr suggested

* It should I that in le fat-soluble vitamin was generally acce led vi ogn zed by its effect on and I s I However Mellanby 919) h d to t agency

Although the above report implies that the lack of fat-soluble vitamins may be responsible for the appearance of stone in rats, subsequent work has not always supported such conclusions. Probably this is due to lack in uniformity of diets and of animals. Di
of
sel
than vitamin A content alter the degree of stone formation.

Jackson[19,20] reviewed the effects of a deficiency of the fat-soluble vitamins on the urinary tract. Davis and Outhouse[8] found a cloudy swelling of the parenchyma in the collecting tubules, but there were no visible calculi. Mori[25] did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues. Black (1923) de-described renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A. Jackson[19] observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A. Some of the kidney tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was attributed to an infection made possible by the lowered resistance. No calculi were found. Fujimaki[9] and Saiki[47] found that concretions appeared sooner
vitamin A than in the
calculi were formed in
min A, inorganic phosphorus and calcium. In 6 rats stone in the bladder (shown by roentgen ray) disappeared after the animals had been placed on a diet rich in vitamin A.

McCarrison[22,23] has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamin A. He believes that in the absence of fat-soluble vitamins certain cereals predispose rats to the formation of vesicle calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast 14.6 per cent developed stones, usually of the $MgNH_4PO_4$ type. The addition of slaked lime caused an increase in the incidence of stones and predisposed to the $CaCO_3$ and $Ca(OH)_2$ type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 0.06 drop of "radiostoleum" sufficed to cause a great decrease in the number of calculi. Experimental $CaCO_3$ stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk (½ ounce per rat daily) to a diet capable of causing urolithiasis in 80 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O BURR PH D AND GRACE MEDES PH D

DIETARY FACTORS IN FORMATION OF URINARY CALCULI

Joly[1] in a review of etiological factors in stone formation states that there is no very conclusive evidence that race or heredity is important A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine Beyond this climate seems to be relatively unimportant In regard to geographical distribution he concludes All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India Mesopotamia and South China) are districts where civilization has existed from the dawn of history and where defective sanitation and hygiene are still the rule The diminution of stone in Europe is undoubtedly the result of improvements in hygiene and dietary

Vitamin Deficiency of Diet —A considerable amount of experimental evidence has accu
tion in lower animals c
begins with the report of
sies of rats 81 cases of calculi were discovered They pointed out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time In a later summary of their work Mendel[33] stated that they found many more cases among their rats on a diet deficient in vitamin A * and stated that when it is recalled that phosphatic calculi deposited in neutral or alkaline urine which in turn frequently owes its reaction to bacterial decomposition are found extensively among peoples living for example in the tropics and Far East on diets quite unlike the mixed regime of most Americans and Europeans the possible relation of the calculi to dietary factors is at once prominently suggested

Although the above report implies that the lack of fat-soluble vitamins may be responsible for the appearance of stone in rats, subsequent work has not always supported such conclusions. Probably this is due to lack in uniformity of diets and of animals. Different workers report the finding of calculi in 20 to 80 per cent of their animals, indicating a large variability in the animals themselves. Furthermore, it has been found that changes in diet, other than vitamin A content, alter the degree of stone formation.

Jackson[12] reviewed the effects of a deficiency of the fat-soluble vitamins on the urinary tract. Davis and Outhouse[4] found a cloudy swelling of the parenchyma in the collecting tubules but there were no visible calculi. Mori[15] did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues. Black (1923) de-described renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A. Jackson[12] observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A. Some of the kidney tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was attributed to an infection made possible by the lowered resistance. No calculi were found. Fujimaki[9] and Suki[17] found that concretions appeared sooner in rats on diets deficient in both protein and vitamin A than in those on diets lacking vitamin A alone. The calculi were formed most quickly in rats on diets deficient in vitamin A, inorganic phosphorus and calcium. In 6 rats stone in the bladder (shown by roentgen ray) disappeared after the animals had been placed on a diet rich in vitamin A.

McCarrison[13, 14] has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamin A. He believes that in the absence of fat soluble vitamins certain cereals predispose rats to the formation of vesicle calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast 14.6 per cent developed stones, usually of the $MgNH_4PO_4$ type. The addition of slaked lime caused an increase in the incidence of stones and predisposed to the $CaCO_3$ and $Ca(OH)_2$ type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 0.06 drop of radiostoleum sufficed to *cause a great decrease in the number of calculi. Experimental* $CaCO_3$ stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk ⅔ ounce per rat daily to a diet capable of causing urolithiasis in 50 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O BURR PH D AND GRACE MEDES PH D

DIETARY FACTORS IN FORMATION OF URINARY CALCULI

JOLY [1] in a review of etiological factors in stone formation states that there is no very conclusive evidence that race or heredity is important A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine Beyond this climate seems to be relatively unimportant In regard to geographical distribution he concludes All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India Mesopotamia and South China) are districts where civilization has existed from the dawn of history and where defective sanitation and hygiene are still the rule The diminution of stone in Europe is undoubtedly the result of improvements in hygiene and dietary

Vitamin Deficiency of Diet A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet This begins with the report of Osborne and Mendel [39] that in 857 necropsies of rats 81 cases of calculi were discovered They pointed out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time In a later summary of their work Mendel[33] stated that they found many more cases among their rats on a diet deficient in vitamin A * and stated that when it is recalled that phosphatic calculi deposited in neutral or alkaline urine which in turn frequently owes its reaction to bacterial decomposition are found ely among peoples living for example in the tropics and ite unlike the mixed regime of most Americans possible relation of the calculi to dietary factors ly suggested

ered that in 19 0 only a single fat-soluble vitamin was was called vitamin A and was recognized by its effect on ptoms leading to xerophthalmia However Mellanby assigned to it a role as an antirachitic agency

Although the above report implies that the lack of fat-soluble vitamins may be responsible for the appearance of stone in rats, subsequent work has not always supported such conclusions. Probably this is due to lack in uniformity of diets and of animals [illegible]

than vitamin A content, alter the degree of stone formation.

Jackson[19,23] reviewed the effects of a deficiency of the fat-soluble vitamins on the urinary tract. Davis and Outhouse[4] found a cloudy swelling of the parenchyma in the collecting tubules but there were no visible calculi. Mori[28] did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues. Black (1923) de-described renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A. Jackson[19] observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A. Some of the kidney tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was attributed to an infection made possible by the lowered resistance. No calculi were found. Fujimaki[9] and Suki[47] found that concretions appeared sooner in rats on diets deficient in both protein and vitamin A than in those on diets lacking vitamin A alone. The calculi were formed most quickly in rats on diets deficient in vitamin A, inorganic phosphorus and calcium. In 6 rats stone in the bladder (shown by roentgen ray) disappeared after the animals had been placed on a diet rich in vitamin A.

McCarrison[27,28] has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamin A. He believes that, in the absence of fat-soluble vitamins, certain cereals predispose rats to the formation of vesical calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast, 14.6 per cent developed stones, usually of the $MgNH_4PO_4$ type. The addition of slaked lime caused an increase in the incidence of stones and predisposed to the $CaCO_3$ and $Ca(OH)_2$ type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 0.06 drop of radiostoleum sufficed to *cause a great decrease in the number of calculi. Experimental* $CaCO_3$ stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk, ¾ ounce per rat daily, to a diet capable of causing urolithiasis in 50 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O BURR PH D AND GRACE MEDES, PH D

DIETARY FACTORS IN FORMATION OF URINARY CALCULI

JOLY,[21] in a review of etiological factors in stone formation, states that there is no very conclusive evidence that race or heredity is important A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine Beyond this, climate seems to be relatively unimportant In regard to geographical distribution, he concludes All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India Mesopotamia and South China) are districts where civilization has existed from the dawn of history and where defective sanitation and hygiene are still the rule The diminution of stone in Europe is undoubtedly the result of improvements in hygiene and dietary

Vitamin Deficiency of Diet —A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet This begins with the report of Osborne and Mendel,[39] that in 857 necropsies of rats, 81 cases of calculi were discovered They pointed out that "in every instance where calculi developed the animals were without an adequate source of fat-soluble vitamin for some time ' In a later summary of their work Mendel[33] stated that they found many more cases among their rats on a diet deficient in vitamin A,* and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living, for example, in the tropics and Far East, on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested "

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O BURR PH D AND GRACE MEDES, PH D

DIETARY FACTORS IN FORMATION OF URINARY CALCULI

JOLY,[21] in a review of etiological factors in stone formation, states that there is no very conclusive evidence that race or heredity is important A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine Beyond this, climate seems to be relatively unimportant In regard to geographical distribution, he concludes All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India Mesopotamia and South China) are districts where civilization has existed from the dawn of history and where defective sanitation and hygiene are still the rule The diminution of stone in Europe is undoubtedly the result of improvements in hygiene and dietary

Vitamin Deficiency of Diet —A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet This begins with the report of Osborne and Mendel,[39] that in 857 necropsies of rats, 81 cases of calculi were discovered They pointed out that "in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time In a later summary of their work Mendel[33] stated that they found many more cases among their rats on a diet deficient in vitamin A,* and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living, for example, in the tropics and Far East, on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested"

Although the above report implies that the lack of fat-soluble vitamins may be responsible for the appearance of stone in rats, subsequent work has not always supported such conclusions. Probably this is due to lack in uniformity of diets and of animals. Different workers report the finding of calculi in 20 to 80 per cent of their animals, indicating a large variability in the animals themselves. Furthermore it has been found that changes in diet other than vitamin A content alter the degree of stone formation.

Jackson[19,20] reviewed the effects of a deficiency of the fat soluble vitamins on the urinary tract. Davis and Outhouse[8] found a cloudy swelling of the parenchyma in the collecting tubules but there were no visible calculi. Mori[23] did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues. Black (1923) de-described renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A. Jackson[19] observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A. Some of the kidney tubules were enormously dilated and filled with casts, cellular detritus or pus. The nephritis was attributed to an infection made possible by the lowered resistance. No calculi were found. Fujimaki[9] and Suzuki[47] found that concretions appeared sooner in rats on diets deficient in both protein and vitamin A than in those on diets lacking vitamin A alone. The calculi were formed most quickly in rats on diets deficient in vitamin A, inorganic phosphorus and calcium. In 6 rats stone in the bladder (shown by roentgen-ray) disappeared after the animals had been placed on a diet rich in vitamin A.

McCarrison[27, 28] has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common. The diets were usually high in cereals, low in vitamin A. He believes that in the absence of fat soluble vitamins certain cereals predispose rats to the formation of vesicle calculi. With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate. No uric acid is present. Of rats on a diet of whole bread and yeast 11.6 per cent developed stones, usually of the $MgNH_4PO_4$ type. The addition of slaked lime caused an increase in the incidence of stones and predisposed to the $CaCO_3$ and $Ca(OH)_2$ type. A vitamin poor vegetable oil in the diet caused a still greater incidence. 0.06 drop of radiostoleum sufficed to *cause a great decrease in the number of calculi. Experimental* $CaCO_3$ stones of rats have the same composition as urinary calculi of cattle. Addition of whole milk ¾ ounce per rat daily to a diet capable of causing urolithiasis in 50 per cent of young rats completely prevented the development of phosphatic calculi. He believes that vitamin A is the factor in milk responsible for these

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O BURR Ph D and GRACE MEDES, Ph D

DIETARY FACTORS IN FORMATION OF URINARY CALCULI

Joly,[21] in a review of etiological factors in stone formation, states that there is no very conclusive evidence that race or heredity is important A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine Beyond this, climate seems to be relatively unimportant In regard to geographical distribution, he concludes All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India, Mesopotamia and South China) are districts where civilization has existed from the dawn of history and where defective sanitation and hygiene are still the rule The diminution of stone in Europe is undoubtedly the result of improvements in hygiene and dietary "

Vitamin Deficiency of Diet —A considerable amount of experi-

out that in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time ' In a later summary of their work Mendel[33] stated that they found many more cases among their rats on a diet deficient in vitamin A * and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living, for example, in the tropics and Far East, on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested '

* It should be remembered that in 1920 only a single fat-soluble vitamin was generally accepted It was called vitamin A and was recognized by its effect on growth and by eye symptoms leading to xerophthalmia However Mellanby (1918 1919) had already assigned to it a role as an antirachitic agency

Although the above report implies that the lack of fat-soluble vitamins may be responsible for the appearance of stone in rats subsequent work has not always supported such conclusions Probably this is due to lack in uniformity of diets and of animals

than vitamin A content, alter the degree of stone formation

Jackson[19,20] reviewed the effects of a deficiency of the fat soluble vitamins on the urinary tract Davis and Outhouse[5] found a cloudy swelling of the parenchyma in the collecting tubules, but there were no visible calculi Mori[35] did not find any abnormality in the kidneys of rats which were so deficient in vitamin A as to cause cornification of many epithelial tissues Black (1923) dedescribed renal enlargement with urate-filled tubules in chicks on diets deficient in vitamin A Jackson[19] observed much nephritis in a colony of rats on a cereal diet which was apparently low in vitamin A Some of the kidney tubules were enormously dilated and filled with casts cellular detritus or pus The nephritis was attributed to an infection made possible by the lowered resistance No calculi were found Fujimaki[9] and Saiki[47] found that concretions appeared sooner
vitamin A than in th
calculi were formed in
min A inorganic phosphorus and calcium In 6 rats stone in the bladder (shown by roentgen ray) disappeared after the animals had been placed on a diet rich in vitamin A

McCarrison has conducted a series of experiments on rats with diets composed of food in general use in areas of India where stone is common The diets were usually high in cereals low in vitamin A He believes that in the absence of fat-soluble vitamins certain cereals predispose rats to the formation of vesicle calculi With cereals or with cereals supplemented with calcium phosphate the calculi are phosphates of calcium and magnesium with traces of oxalate No uric acid is present Of rats on a diet
of whole bread and
of the $MgNH_4PO_4$ t
increase in the incid
and $Ca(OH)_2$ type
a still greater incide
cause a great decre
$CaCO_3$ stones of rats have the same composition as urinary calculi of cattle Addition of whole milk ½ ounce per rat daily to a diet capable of causing urolithiasis in 50 per cent of young rats completely prevented the development of phosphatic calculi He believes that vitamin A is the factor in milk responsible for these

CHAPTER XVII

BIOLOGICAL AND CHEMICAL FACTORS IN STONE FORMATION

By GEORGE O BURR Ph D and GRACE MEDES, Ph D

DIETARY FACTORS IN FORMATION OF URINARY CALCULI

Joly,[31] in a review of etiological factors in stone formation, states that there is no very conclusive evidence that race or heredity is important. A low humidity and high temperature may hasten stone formation in those who are predisposed by increasing the concentration of the urine. Beyond this, climate seems to be relatively unimportant. In regard to geographical distribution, he concludes "All we can say is that lithiasis is more usual in the Old World than in the New and that the three most important stone areas (India, Mesopotamia and South China) are districts where civilization has existed from the dawn of history and where defective sanitation and hygiene are still the rule. The diminution of stone in Europe is undoubtedly the result of improvements in hygiene and dietary."

Vitamin Deficiency of Diet.—A considerable amount of experimental evidence has accumulated which indicates that stone formation in lower animals can be controlled largely by diet. This begins with the report of Osborne and Mendel,[32] that in 857 necropsies of rats 81 cases of calculi were discovered. They pointed out that "in every instance where calculi developed the animals were without an adequate source of fat soluble vitamin for some time." In a later summary of their work Mendel[33] stated that they found many more cases among their rats on a diet deficient in vitamin A,* and stated that "when it is recalled that phosphatic calculi deposited in neutral or alkaline urine, which in turn frequently owes its reaction to bacterial decomposition, are found extensively among peoples living for example, in the tropics and Far East on diets quite unlike the mixed régime of most Americans and Europeans, the possible relation of the calculi to dietary factors is at once prominently suggested."

varied from 0 to 8 per cent (replacing Crisco). As a control diet free from vitamin A she fed a mixture of purified casein, starch, yeast and salts. She found calculi visible to the naked eye in rats on diets very low in vitamin A (0 per cent butter) but not in rats on highly purified vitamin A free diets. She believes that very early death prevented growth to macroscopic size, although she does not mention having made any microscopic study. Therefore, she concludes that a partial deficiency in vitamin A favors large calculi more than an absolute deficiency. The possibility that the high wheat diet may have also favored stone formation is not discussed.

Perlmann and Weber[illegible] found phosphatic stones in the bladders of 23 per cent of rats fed on vitamin A deficient diet. Another group of 100 rats were fed limited quantities of a diet of scraps, milk and carrots so that they grew to only 120 gm. while the controls (20 animals) grew to 220 gm. in weight. 50 died within three months while 29 lived one hundred and eighty days. Seven showed gravel at the end of this period. The small stones consisted of urates and resembled those of human beings. All normally fed rats were free from stone. They conclude that vitamin A deficiency is not the only factor but is an important one. Europeans have a predominance of urate stones while oxalate stones predominate among the Japanese. In the case of children, stones are probably due to improper feeding, but in adults anatomical factors, infections and disordered metabolism are the probable causes.

In most of the experiments thus far mentioned, both of the fat soluble vitamins A and D were low, but the occurrence of calculi was ascribed by the workers to a deficiency of A only. Dixon and Hoyle[illegible] fed two groups of half grown rats an adequate basal ration and in addition gave them 11 and 17 mg. daily of irradiated ergosterol in cacao butter. Those on the smaller dose grew normally, while those on the larger dose grew only slowly. Autopsy showed no pathological lesions except in the urinary tract. Almost without exception calcium phosphate calculi were found. Since vitamin A was plentiful, it was suggested that with excess of vitamin D larger amounts of calcium and phosphorus are excreted than the urine can dissolve. They believe that a large excess of vitamin D in the presence of very little vitamin A would give a tendency toward calculi and in the tropics where there is much ultra violet exposure and the diet is low in vitamin A, phosphatic concretions should be very common.

Usui[illegible] reared rabbits on a diet deficient in the fat-soluble vitamins A and D (ground barley, casein, lard, salts, oryzanin and radish juice). He ran controls on a normal rabbit ration, okara. Of 43 animals on the basal ration alone for thirty five to one hundred and seven days, 7 per cent indicated gall stones, 17 per cent

nephroliths and 2 per cent both. The nephroliths contained calcium oxalates and phosphates. Limited data indicate greater frequency in the right kidney. There were definite symptoms of vitamin A deficiency in many. But only 65 per cent of the animals with calculi developed eye trouble. He believes that there are at least two factors and that calculus formation is closely related to vitamin D.

I Sumi[54] attempted to find the effects of vitamin A deficiency on the blood serum of rabbits which might account for the appearance of stones. Sodium, potassium, calcium, magnesium, cholesterol and fatty acids were determined. Those cases which developed xerophthalmia showed a marked increase in serum calcium. If calculi appeared, all blood constituents increased, calcium and cholesterol increasing most. Calculi appeared in some cases where symptoms of avitaminosis were lacking.

Abderhalden (1931) reports an unusually large number of sarcomas and urinary bladder stones in rats fed a diet of milk and rice. This diet permits the animals to reach an advanced age, but pellagra like symptoms often occur. The diet probably is not very low in vitamin A.

Pontius, Carr and Doyle[48] report that calculi in the urinary tract of sheep are largely calcium phosphate and aluminum silicate. When sheep have calculi the urine from their bladders is always strongly alkaline. They believe that high alkalinity aids calculus formation as it favors precipitation of earthy phosphates. They studied the effect of diet on the pH and ash of sheeps urine. With a pure alfalfa diet the urine would reach a pH of 9 and an ash content of 11 per cent.

Easterfield and Bruce[8] report xanthine calculi in the kidneys of some New Zealand sheep. They attribute these stones to a deficiency of minerals in the pasturage.

Mineral Unbalance of Diet.—In view of the present state of the literature pertaining to the experimental production of calculi, only tentative conclusions can be drawn as to the relative importance of the several dietary factors now thought to play a role in stone formation. The lack of vitamin A has produced calculi in a large number of experiments, but it has frequently failed to do so. An increase of calcium in the diet increases the incidence of stone in the absence of vitamin A, and in some cases a high calcium diet produces stone even when vitamin A is plentiful. Cattle and sheep living on alfalfa, grass and other green pasturage certainly receive an abundance of vitamin A. Nevertheless calculi frequently occur in their urinary tracts. Infection of the urinary tract produces an alkaline reaction which is favorable to the precipitation of the

earthy phosphates (Hellström[19]) and frequently leads to the depositing of calculi with organic nuclei Consequently the effect of diet on the pH of the urine should always be considered

As Joly[21] has pointed out calculi as they occur in man can hardly be considered as due solely to an excess of the stone-forming substance in the diet Seventy-eight per cent of the stones removed at the Canton Hospital were composed of uric acid or urates yet

that stone formation is really a deficiency disease rather than the

shown that experimental stones in rats are made of magnesium ammonium phosphate instead of calcium carbonate when no lime is added to a cereal diet

With one exception the experimental stones in rats and rabbits

to date have not thrown much light on the cause of these calculi in man

The only experiment in which urate calculi have been reported is that of Erdmann and Weber[4] It will be recalled that these rats were greatly emaciated and were suffering from underfeeding rather than any specific vitamin deficiency This would indicate that all types of calculi are at least partially due either to a dietary deficiency or to a low level of nutrition

CHEMICAL FACTORS IN STONE FORMATION

Colloidal Precipitation —The role of mucus or other colloidal binder in certain types of concretions has been recognized since the time of Hippocrates and Galen A von Heyde (1684) initiated experimental work by dissolving out the crystalline salts of urinary calculi and observing the framework and Hemsbach[15] stated that this framework was unquestionably necessary for true stone formation since otherwise urinary salts can only yield crystalline pulverulent or granular precipitates This point of view became widely accepted although it was recognized that certain stones of non inflammatory origin such as uric acid stones in the kidney and bladder and cholesterol stones in the gall bladder might occasionally be found in which no organic binder could be demonstrated It remained for colloidal chemistry under the leadership

nephroliths and 2 per cent both The nephroliths contained calcium oxalates and phosphates Limited data indicate greater frequency in the right kidney There were definite symptoms of vitamin A deficiency in many But only 65 per cent of the animals with calculi developed eye trouble He believes that there are at least two factors and that calculus formation is closely related to vitamin D

Usui[54] attempted to find the effects of vitamin A deficiency on the blood serum of rabbits which might account for the appearance of stones Sodium potassium calcium magnesium cholesterol and fatty acids were determined Those cases which developed xerophthalmia showed a marked increase in serum calcium If calculi appeared all blood constituents increased calcium and cholesterol increasing most Calculi appeared in some cases where *symptoms of avitaminosis were lacking*

Abderhalden (1931) reports an unusually large number of sarcomas and urinary bladder stones in rats fed a diet of milk and rice This diet permits the animals to reach an advanced age but pellagra like symptoms often occur The diet probably is not very low in vitamin A

Pontius Carr and Doyle[43] report that calculi in the urinary tract of sheep are largely calcium phosphate and aluminum silicate When sheep have calculi the urine from their bladders is always strongly alkaline They believe that high alkalinity aids calculus formation as it favors precipitation of earthy phosphates They studied the effect of diet on the pH and ash of sheeps urine With a pure alfalfa diet the urine would reach a pH of 9 and an ash content of 11 per cent

Easterfield and Bruce[8] report xanthine calculi in the kidneys of some New Zealand sheep They attribute these stones to a deficiency of minerals in the pasturage

Mineral Unbalance of Diet —In view of the present state of the literature pertaining to the experimental production of calculi only tentative conclusions can be drawn as to the relative importance of the several dietary factors now thought to play a role in stone formation The lack of vitamin A has produced calculi in a large number of experiments but it has frequently failed to do so An increase of calcium in the diet increases the incidence of stone in the absence of vitamin A and in some cases a high calcium diet produces stone even when vitamin A is plentiful Cattle and sheep living on alfalfa grass and other green pasturage certainly receive an abundance of vitamin A Nevertheless calculi frequently occur in their urinary tracts Infection of the urinary tract produces an alkaline reaction which is favorable to the precipitation of the

earthy phosphates (Hellström[illegible]) and frequently leads to the depositing of calculi with organic nuclei. Consequently the effect of diet on the pH of the urine should always be considered.

As Joly[illegible] has pointed out, calculi as they occur in man can hardly be considered as due solely to an excess of the stone-forming substance in the diet. Seventy-eight per cent of the stones removed at the Canton Hospital were composed of uric acid or urates, yet the people subsist largely on rice which is nearly purine-free. In general, calculi are common only where the diet is very monotonous and are uncommon where the diet is varied. This fact indicates that stone formation is really a deficiency disease rather than the result of an excess of stone forming materials in the diet. However it seems clear that the composition of the diet affects the composition of the stones (McCarrison, Van Leersum). Ranganathan[illegible] has shown that experimental stones in rats are made of magnesium ammonium phosphate instead of calcium carbonate when no lime is added to a cereal diet.

With one exception, the experimental stones in rats and rabbits have been reported to be largely calcium, magnesium and ammonium phosphates, carbonates and oxalates. Since a large percentage of human stones are composed of uric acid and urates, the experiments to date have not thrown much light on the cause of these calculi in man.

The only experiment in which urate calculi have been reported is that of Perlmann and Weber[illegible]. It will be recalled that these rats were greatly emaciated and were suffering from underfeeding rather than any specific vitamin deficiency. This would indicate that all types of calculi are at least partially due either to a dietary deficiency or to a low level of nutrition.

CHEMICAL FACTORS IN STONE FORMATION

Colloidal Precipitation. The role of mucus or other colloidal binder in certain types of concretions has been recognized since the time of Hippocrates and Galen. A. von Heyde (1684) initiated experimental work by dissolving out the crystalline salts of urinary calculi and observing the framework, and Hemsbach[illegible] stated that this framework was unquestionably necessary for true stone formation since otherwise urinary salts can only yield crystalline pulverulent or granular precipitates. This point of view became widely accepted, although it was recognized that certain stones of non-inflammatory origin, such as uric acid stones in the kidney and bladder and cholesterol stones in the gall-bladder, might occasionally be found in which no organic binder could be demonstrated. It remained for colloidal chemistry under the leadership

nephroliths and 2 per cent both The nephroliths contained calcium oxalates and phosphates Limited data indicate greater frequency in the right kidney There were definite symptoms of vitamin A deficiency in many But only 65 per cent of the animals with calculi developed eye trouble He believes that there are at least two factors and that calculus formation is closely related to vitamin D

Usuni[54] attempted to find the effects of vitamin A deficiency on the blood serum of rabbits which might account for the appearance of stones Sodium potassium calcium magnesium cholesterol and fatty acids were determined Those cases which developed xerophthalmia showed a marked increase in serum calcium If calculi appeared all blood constituents increased calcium and

comas and urinary bladder stones in rats fed a diet of milk and rice This diet permits the animals to reach an advanced age but pellagra like symptoms often occur The diet probably is not very low in vitamin A

Pontius Carr and Doyle[43] report that calculi in the urinary tract of sheep are largely calcium phosphate and aluminum silicate When sheep have calculi the urine from their bladders is always strongly alkaline They believe that high alkalinity aids calculus formation as it favors precipitation of earthy phosphates They studied the effect of diet on the pH and ash of sheeps urine With a pure alfalfa diet the urine would reach a pH of 9 and an ash content of 11 per cent

Easterfield and Bruce[5] report xanthine calculi in the kidneys of some New Zealand sheep They attribute these stones to a deficiency of minerals in the pasturage

Mineral Unbalance of Diet —In view of the present state of the literature pertaining to the experimental production of calculi only tentative conclusions can be drawn as to the relative importance of the several dietary factors now thought to play a role in stone formation The lack of vitamin A has produced calculi in a large number of experiments but it has frequently failed to do so An increase of calcium in the diet increases the incidence of stone in the absence of vitamin A and in some cases a high calcium diet produces stone even when vitamin A is plentiful Cattle and sheep living on alfalfa grass and other green pasturage certainly receive an abundance of vitamin A Nevertheless calculi frequently occur in their urinary tracts Infection of the urinary tract produces an alkaline reaction which is favorable to the precipitation of the

earthy phosphates (Hellström[14]) and frequently leads to the deposit ing of calculi with organic nuclei. Consequently the effect of diet on the pH of the urine should always be considered.

As Joly[31] has pointed out, calculi as they occur in man can hardly be considered as due solely to an excess of the stone-forming substance in the diet. Seventy-eight per cent of the stones removed at the Canton Hospital were composed of uric acid or urates, yet

that stone formation is really a deficiency disease rather than the result of an excess of stone forming materials in the diet. However it seems clear that the composition of the diet affects the composition of the stones (McCarrison, Van Leersum). Ranganathan[45] has shown that experimental stones in rats are made of magnesium ammonium phosphate instead of calcium carbonate when no lime is added to a cereal diet.

With one exception the experimental stones in rats and rabbits have been reported to be largely calcium, magnesium and ammonium phosphates, carbonates and oxalates. Since a large percentage of human stones are composed of uric acid and urates, the experiments to date have not thrown much light on the cause of these calculi in man.

The only experiment in which urate calculi have been reported is that of Perlmann and Weber.[42] It will be recalled that these rats were greatly emaciated and were suffering from underfeeding rather than any specific vitamin deficiency. This would indicate that all types of calculi are at least partially due either to a dietary deficiency or to a low level of nutrition.

CHEMICAL FACTORS IN STONE FORMATION

Colloidal Precipitation. The role of mucus or other colloidal binder in certain types of concretions has been recognized since the time of Hippocrates and Galen. A. van Heyde (1684) initiated experimental work by dissolving out the crystalline salts of urinary calculi and observing the framework, and Heinsbach[3] stated that this framework was unquestionably necessary for true stone formation, since otherwise urinary salts can only yield crystalline pulverulent or granular precipitates. This point of view became widely accepted, although it was recognized that certain stones of non-inflammatory origin, such as uric acid stones in the kidney and bladder and cholesterol stones in the gall bladder, might occasionally be found in which no organic binder could be demonstrated. It remained for colloidal chemistry under the leadership

nephroliths and 2 per cent both The nephroliths contained calcium oxalates and phosphates Limited data indicate greater frequency in the right kidney There were definite symptoms of vitamin A deficiency in many But only 65 per cent of the animals with calculi developed eye trouble He believes that there are at least two factors and that calculus formation is closely related to vitamin D

Usuni[44] attempted to find the effects of vitamin A deficiency on the blood serum of rabbits which might account for the appearance of stones Sodium potassium calcium magnesium cholesterol and fatty acids were determined Those cases which developed xerophthalmia showed a marked increase in serum calcium If calculi appeared all blood constituents increased calcium and cholesterol increasing most Calculi appeared in some cases where symptoms of avitaminosis were lacking

Abderhalden (1931) reports an unusually large number of sarcomas and urinary bladder stones in rats fed a diet of milk and rice This diet permits the animals to reach an advanced age but pellagra like symptoms often occur The diet probably is not very low in vitamin A

Pontius Carr and Doyle[43] report that calculi in the urinary tract of sheep are largely calcium phosphate and aluminum silicate When sheep have calculi the urine from their bladders is always strongly alkaline They believe that high alkalinity aids calculus formation as it favors precipitation of earthy phosphates They studied the effect of diet on the pH and ash of sheeps urine With a pure alfalfa diet the urine would reach a pH of 9 and an ash content of 11 per cent

Easterfield and Bruce[8] report xanthine calculi in the kidneys of some New Zealand sheep They attribute these stones to a deficiency of minerals in the pasturage

Mineral Unbalance of Diet —In view of the present state of the literature pertaining to the experimental production of calculi only tentative conclusions can be drawn as to the relative importance of the several dietary factors now thought to play a role in stone formation The lack of vitamin A has produced calculi in a large number of experiments but it has frequently failed to do so An increase of calcium in the diet increases the incidence of stone in the absence of vitamin A and in some cases a high calcium diet produces stone even when vitamin A is plentiful Cattle and sheep living on alfalfa grass and other green pasturage certainly receive an abundance of vitamin A Nevertheless calculi frequently occur in their urinary tracts Infection of the urinary tract produces an alkaline reaction which is favorable to the precipitation of th

earthy phosphates (Hellstrom[14]) and frequently leads to the depositing of calculi with organic nuclei Consequently the effect of diet on the pH of the urine should always be considered

As Joly[21] has pointed out calculi as they occur in man can hardly be considered as due solely to an excess of the stone-forming substance in the diet Seventy-eight per cent of the stones removed at the Canton Hospital were composed of uric acid or urates yet the people subsist largely on rice which is nearly purine free In general calculi are common only where the diet is very monotonous and are uncommon where the diet is varied This fact indicates that stone formation is really a deficiency disease rather than the [illegible]

shown that experimental stones in rats are made of magnesium ammonium phosphate instead of calcium carbonate when no lime is added to a cereal diet

With one exception the experimental stones in rats and rabbits have been reported to be largely calcium magnesium and ammonium phosphates carbonates and oxalates Since a large percentage of human stones are composed of uric acid and urates the experiments to date have not thrown much light on the cause of these calculi in man

The only experiment in which urate calculi have been reported is that of Perlmann and Weber[4] It will be recalled that these rats were greatly emaciated and were suffering from underfeeding rather than any specific vitamin deficiency This would indicate that all types of calculi are at least partially due either to a dietary deficiency or to a low level of nutrition

CHEMICAL FACTORS IN STONE FORMATION

Colloidal Precipitation The role of mucus or other colloidal binder in certain types of concretions has been recognized since the time of Hippocrates and Galen A von Heyde (1684) initiated experimental work by dissolving out the crystalline salts of urinary calculi and observing the framework and Hemsbach stated that this framework was unquestionably necessary for true stone formation since otherwise urinary salts can only yield crystalline pulverulent or granular precipitates This point of view became widely accepted although it was recognized that certain stones of non inflammatory origin such as uric acid stones in the kidney and bladder and cholesterol stones in the gall bladder might occasionally be found in which no organic binder could be demonstrated It remained for colloidal chemistry under the leadership

of Schade[49] and Aschoff[1] following the early experiments of Ord[38] to demonstrate that the same colloidal processes occur in all stone formation Schade[51] postulated that the fundamental step in calculus formation is the irreversible precipitation of some hydrophilic collid which may (Type I) remain as a pure colloid concretion or (Type II) become the matrix in which crystalloids of different origin form varying amounts of the stone or (Type III) subsequently undergo crystallization with the formation of a pure crystalloid concretion

Role of Urinary Colloids in Kidney Stone Formation —Morner[36] investigated the colloids of normal urine and identified an albumin which he believed to be identical with serum albumin chondroitin sulphuric acid and nucleic acid Salkowski[45] isolated a non-diffusible carbohydrate containing a nitrogen complex Various estimates have been made of the total amount of these colloids present Lichtwitz (1914) dialyzed urine against distilled water and estimated the amount of colloids remaining undialyzed He found an average of 0 85 gm of colloid per liter of urine

There is little evidence that the colloids of normal urine form the matrix of urinary calculi but rather that they act as protective colloids stabilizing the solution Calculi of Type II are usually classified as being of inflammatory origin Schade[51] classified Type I as originating without inflammation but Troltzsch[53] in reviewing all the known cases has showed that in all but 3 questionable instances either infection of the kidney or some pathological state was present Moreover it seems more logical that Types I and II occur under similar conditions except that in the latter case the urine is also supersaturated with some crystalloid constituent which

date 25 cases had been reported Troltzsch groups these calculi in three classes (*a*) albuminous (including those composed of fibrin) (*b*) bacterial and (*c*) amyloid Of the 29 cited 13 were of *a* 12 Th f *a* and *b* grade o er nto each other and ance

The crystalloids whic may ... as of mixed Type II are uric acid and the urates calcium oxalate the phosphates of calcium magnesium and ammonium calcium carbonate cystine—all substances may be present in urine in larger quantities than would l from their solubilities in water For inst Gudz solubility of uric acid at C as 65 er approximately twenty

times this amount may be excreted by a normal individual in twenty-four hours Seidell[52] records the solubility of calcium oxalate

in maintaining various crystalloids in their supersaturated state has been investigated by numerous workers Pauli and Samec[40] compared the solubilities of various substances in distilled water with their solubilities in blood serum and in 1 5 per cent albumin solution and gave the following figures

TABLE 25

	Solubility in gm at 25° C in 100 gm solution		
	H_2O gm	Serum gm	1 5 per cent gelatin gm
Calcium phosphate ($Ca_3(PO_4)_2$)	0 011	0 0[illegible]1	0 018
Calcium carbonate	0 004	0 0[illegible]3	0 015
Uric acid	0 040	0 057	

Joly[21] states that if a specimen of urine is dialyzed through a parchment membrane against a large quantity of water the crystalloids will diffuse through the membrane while the colloids will be left behind If this solution of the urinary crystalloids is slowly

centrating the dialysate to the volume of the original urine there was no precipitation, provided the original acidity was maintained

The Peptizing Action of Urea —Another substance whose capacity to increase the solubility of other constituents of urine should be considered is urea As the unsaturated amide of carbonic acid, urea combines with acids to form salt-like compounds, many of which are highly soluble The nitrate and the oxalate are well known DuToit[7] identified seven other such compounds of urea with oxalic acetic, hydrochloric, nitric and sulphuric acids all except $Ur\,HNO_3$ being highly soluble Urea also forms additional compounds with salts probably through the residual valence of its oxygen For instance, 1, 2, 3, 4 or more molecules of urea may unite with calcium chloride to form a series of more or less unstable hygroscopic salts Many strains of staphylococci the most common organisms in calcareous kidneys are urea-splitting and hence by the formation of ammonia produce an alkaline urine in which

of Schade[49] and Aschoff[1] *following the early experiments of Ord*[33] to demonstrate that the same colloidal processes occur in all stone formation Schade[51] postulated that the fundamental step in cal culus formation is the irreversible precipitation of some hydrophilic collid which may (Type I) remain as a pure colloid concretion or (Type II) become the matrix in which crystalloids of different origin form varying amounts of the stone or (Type III) subsequently undergo crystallization with the formation of a pure crystalloid concretion

Rôle of Urinary Colloids in Kidney Stone Formation —Morner[38] investigated the colloids of normal urine and identified an albumin which he believed to be identical with serum albumin chondroitin sulphuric acid and nucleic acid Salkowski[48] isolated a non-diffus ible carbohydrate containing a nitrogen complex Various esti mates have been made of the total amount of these colloids present Lichtwitz (1914) dialyzed urine against distilled water and estimated the amount of colloids remaining undialyzed He found an average of 0 85 gm of colloid per liter of urine

There is little evidence that the colloids of normal urine form the matrix of urinary calculi but rather that they act as protective colloids stabilizing the solution Calculi of Type II are usually classified as being of inflammatory origin Schade[51] classified Type I as originating without inflammation but Troltzsch[53] in reviewing all the known cases has showed that in all but 3 questionable instances either infection of the kidney or some pathological state was present Moreover it seems more logical that Types I and II occur under similar conditions except that in the latter case the urine is also supersaturated with some crystalloid constituent which is carried down with the lyophilic colloid as it coagulates

Troltzsch[53]
nd added
] that to

date 25 cases had been reported Troltzsch groups these calculi in three classes (*a*) albuminous (including those composed of fibrin) (*b*) bacterial and (*c*) amyloid Of the 29 cited 13 were of *a* 12 of *b* and 4 of *c* Those of *a* and *b* grade over into each other and according to him albumin or fibrin supplies *the ground substance* for both the bacterial and the amyloid

The crystalloids which may be present in the concretions of mixed Type II are uric acid and the urates calcium oxalate the phosphates of calcium magnesium and ammonium calcium car bonate cystine—all substances which may be present in urine in larger quantities than

water For instance
37° C as 65 mg per

times this amount may be excreted by a normal individual in twenty four hours Seidell[5] records the solubility of calcium oxalate at 21° C as 6 8 mg per liter of [illegible]

in maintaining various crystalloids in their supersaturated state has been investigated by numerous workers Pauli and Samec[40] compared the solubilities of various substances in distilled water with their solubilities in blood serum and in 1 5 per cent albumin solution and gave the following figures

TABLE 25

	Solubility in gm at 25° C in 100 gm solution		
	H_2O gm	Serum gm	1 5 per cent gelatin gm
Calcium phosphate ($Ca_3(PO_4)_2$)	0 011	0 0 1	0 018
Calcium carbonate	0 004	0 023	0 015
Uric acid	0 040	0 057	

Joly[1] states that if a specimen of urine is dialyzed through a parchment membrane against a large quantity of water the crystalloids will diffuse through the membrane while the colloids will be left behind If this solution of the urinary crystalloids is slowly evaporated down it will be found that a copious deposit forms long before the solution is concentrated to the original volume of the urine These findings were not substantiated by Newcomb[17] who repeated the experiment and found that uric acid distributed itself evenly on both sides of the membrane and hence could not be attached to the urinary colloids Moreover he found that on concentrating the dialysate to the volume of the original urine there was no precipitation provided the original acidity was maintained

The Peptizing Action of Urea —Another substance whose capacity to increase the solubility of other constituents of urine should be considered is urea As the unsaturated amide of carbonic acid, urea combines with acids to form salt like compounds many of which are highly soluble The nitrate and the oxalate are well known DuToit[7] identified seven other such compounds of urea with oxalic acetic hydrochloric nitric and sulphuric acids all except Ur HNO_3 being highly soluble Urea also forms additional compounds with salts probably through the residual valence of its oxygen For instance 1, 2 3, 4 or more molecules of urea may unite with calcium chloride to form a series of more or less unstable hygroscopic salts Many strains of staphylococci the most common organisms in calcareous kidneys are urea-splitting and hence by the formation of ammonia produce an alkaline urine in which

the solubility of phosphates is low, and at the same time deprive the urine of urea, one of its stabilizing factors

One of the authors (G M) tested the solubility of calcium oxalate and uric acid in solutions of urea and found that urea exerts a peptizing effect, increasing the solubility of the oxalate from 0 63 mg per 100 cc of solution (in water) to 8 02 mg per 100 cc of solution (in 50 per cent urea), and producing a slight increase in solubility of uric acid

TABLE 26 —SOLUBILITY OF CALCIUM OXALATE IN AQUEOUS SOLUTIONS OF UREA *(100 MG OF CALCIUM OXALATE $CaC_2O_4 H_2O$ + UREA AND MADE UP TO 100 CC* WITH WATER) (THE SOLUBILITY OF URIC ACID IS EXPRESSED IN MG PER 100 CC OF SOLUTION) TEMPERATURE 22 6° C

Urea (gm)		0 06	0 15	0 80	3 00	16 00	50 00
Solubility $CaC_2O_4 H_2O$	0 63	0 60	0 70	0 82	1 28	2 80	8 02

TABLE 27 —SOLUBILITY OF URIC ACID IN SOLUTIONS OF UREA GRAMS OF UREA + 80 MG URIC ACID MADE UP TO 100 CC WITH CO_2 FREE WATER THE SOLUBILITY *OF URIC ACID IS EXPRESSED IN MG PER 100 CC* OF SOLUTION *TEMPERATURE 26 2° C*

Urea gm	Solubility uric acid mg	Urea gm	Solubility uric acid mg	Urea gm	Solubility uric acid mg
	4 39	6 00	9 21	16 00	8 59
0 16	4 78	8 00	9 73	18 00	7 80
0 40	5 33	10 00	11 52	20 00	7 68
2 00	6 44	12 00	10 67	80 00	7 12
4 00	6 83	14 00	9 30		

The rise in solubility of calcium oxalate in solutions of urea is continuous, indicating that there is some peptizing action but that molecular combinations are not formed When urea is present to the extent of 3 per cent, the amount of calcium oxalate which may be held in solution is doubled Fifteen hundred cc of urine, saturated with *calcium oxalate and containing 3 per cent urea* would contain 19 mg calcium oxalate an amount approximating the average daily output of a normal individual

The increase of solubility of uric acid is insufficient to account for the amount which may be present in normal urine, since in a volume of 1500 cc containing 3 per cent urea only about 100 mg of uric acid could be dissolved, whereas 250 mg to 1 gm might be excreted Gudzent[11] found the solubility of potassium urate to be 2 7002 gm per liter of solution at 37° C of sodium urate as 1 5043 gm and of ammonium urate as 0 7413 gm per liter, but since all the acid

reached,

ed

m

phosphate buffer mixtures containing borates and found that at pH 6 4 the solubility was 0 1123 gm per liter of solution at 37° C , as compared with 0 0328 gm per liter at pH 5 4 At pH 7 4 the

solubility was 0 911 gm per liter and at pH 8 3 56 gm per liter Harpuder and Erbsen[1?] investigated the solubility of uric acid in various buffer mixtures using Na^+ as the cation They reported that at any given pH the solubility was affected by the nature of the anions composing the buffer solution Assuming Jung s findings hold for urine, even at pH 6 4 the increased solubility due to salt formation together with the peptizing action of urea on the free acid (about 97 per cent of the total) would account for all the uric acid of normal urine provided the output of uric acid is low and the diuresis moderately large (about 1500 cc) At a pH of 7 4 *the solubility would be sufficiently increased by these two factors to account for the maximum normal output (of about 1 gm)*

Physico-chemical Studies —Effect of pH —The extensive work of Schade has given us an insight into the physico-chemical laws governing the formation of pure crystalloid stones (Type III) He has showed[50] that from a supersaturated solution of uric acid more acid than pH 5 5 or of sodium urate more alkaline than pH 7 well-formed crystals appear but within a zone between 5 5 to 7 uric acid separates in droplets discernible only by means of the ultra-microscope If this guttulate separation is not disturbed by too

op-
are
of

crystallization become radially marked firm spheroliths Since growth in these stones is frequently continuous by the constant addition of droplets the structure of such stones is generally homogeneous throughout their entire mass and layering is frequently absent

Uric acid undergoes this preliminary guttulate separation from pure aqueous solution but oxalates require the presence of precipitable colloids Ord[38] early described radially striated balls of oxalates in gelatin solutions and Hatschek[13] produced them also from solutions of agar Schade states that similar observations exist with regard to calcium carbonate

Weiser and Gray[40] contend that the conditions are more complex,

shifts in the pH of the urine Meyer (1929) investigated the

conditions under which the various deposits may be formed He gives the following

pH	Type of calculus
About 5	Pure uric acid
6	Mixed, of pure dense uric acid, urate, oxalate and Ca phosphate
7	Ca phosphate
8–7	Hard stratified calculi, chiefly of $MgNH_4PO_4$, Ca phosphate and NH_4 urate in ammoniacal urine (deposit slowly)
8	Soft free calculi, chiefly $MgNH_4PO_4$ $CaCO_3$ and NH_4 urate (deposit rapidly) Considerable amounts of $CaCO_3$ indicate highly alkaline urine

Pure crystalline stones of unmixed type also show a tendency to banding although a radial structure of the crystals is more pronounced This banding occurs most frequently when numerous small stones are present as for instance, in multiple gall stone formation and Schade[51] attributes the layering to a flattening of the added droplets before crystallization due to the pressure of neighboring stones The remarkable regularity of the bands have suggested to colloid chemists the similarity to Liesegang s rings which Liesegang produced by the precipitation of silver chromate when he allowed silver nitrate to diffuse into a gelatin gel containing dichromate Schade s objection to this explanation was based upon his idea that precipitation of bands could not occur with such rhythmic regularity when preformed crystals offered points of resistance to diffusion Weiser and Gray[59] however, reproduced the phenomenon in gelatin gels containing minute crystals of cholesterol, even when the concentration of gelatin was as low as 0 05 per cent They conclude by their experiments that the rhythmic precipitation takes place in the mass of minute crystals and that the gelatin jelly merely serves to inhibit their growth and so to maintain a mass of fine crystals in which the diffusion and precipitation may occur

ζ Potential Mere supersaturation of urine with colloid capable of irreversible coagulation does not necessarily cause stone formation, the effects not only of other protective colloids but also of electrolytes must be considered Powis[44] has shown that when colloids [illegible] coagu- termed poten- [illegible]ginning an extensive study of the physico-chemical laws of gall stone for-

mation have measured the effects of an ons and cations an l of H^+ and OH on the ζ potential They showed that monovalent cations such as Na^+ and K^+ increase the potential when present in small amounts and decrease it to the critical zone only when present in comparat vely h gh concentrations The divalent ions Ba^{++} Ca^{++} and Mg^{++} produce a slighter initial increase and smaller amounts are required to lower the potential to the cr tical zone than with monovalent ions The trivalent ion Al^{+++} produces an immed ate lowering toward the zero zone in wh ch the colloid loses its stab lity and flocculates In h gher concentrations of the

one another follo ving the lyotrop c series as showed by Briggs[4] the greater the movement velocity the smaller the ζ potent al m in series Li^+ Na^+ K^+ Rb^+ NH_4^+ and Cs^+ lower concentra

favorable for coagulat on of any irreversibly precipitat ng colloid present in the ur ne

REFERENCES

1 Aschoff L 1913 W e entstehen d e re nen Cholesterinste ne? Münch med Wchnschr, 60 1753-1756

2 Batchelder, E L 1923 Dissertat on, Columb a University New York, 19?9 The effect of success ve diminut on of vitamin A in the food on the nutr t on and vital ty of alb no rats

3 Beach J R 19 3 V tamin A deficiency in poultry Science N S 58 542

4 Briggs, D R 19?8 The ζ potential and the lyotrop c series J Phys Chem 32 1646-1662

19 ——— 1925 The Effects of Inanition and Malnutrition upon

lanition and of
78 8 81 122 8

25 ——— 1928 Experimental production of stone in bladder Indian J Med Res 15 801 806
26 ——— 1930 Influence of lime in favoring stone in the bladder in rats Indian J Med Res 17 1101 1102
27 ——— 1930 Relative potency of certain cereal grains in favoring formation of stone in rats Indian J Med Res 17 1103 1107
28 ——— 1931 Further researches on stone Indian J Med Res 18 903 934

20 212–217

on Sedimenten und die Bildung

n the influence of colloids
mixtures of colloids with

39 OSBORNE T B AND MENDEL, I B 1917 The incilence of pl osphatic urinary calculi in rats fed on experimental rations J Am Med Assn 69 32 33
40 PAULI WO AND SAMEC M 1909 Ueber Loslichkeitsbeeinflussung von Elektrolyten durch Eiweisskörper I Biochem Ztschr 17 235-256
41 PEDROSO G 1930 Albumin and fibrin calculi of the kidney J Urol 23 627-638
42 PERLMANN S AND WEBER W 1930 Zur experimentellen Blasen steinerzeugung Munch med Wchnschr 77 680-681
43 PONTIUS B E CARR R. H AND DOYLE L P 1931 Urinary calculi in sheep J Agric Res 42 433-446
44 POWIS I B 1915 Die Beziehung zwischen der Bestandigkeit einer ... renzflache und die ... 89 156-212 ... urinary calculi in

46 RICHARDS I W McCAFFREY C I AND BISBEE H 1901 Die Okklusion von Magnesiumoxalate durch Calciumoxalate und die Löslichkeit von Calciumoxalate Ztschr f anorg Chem 28 85
47 SAIKI T 1927 Disposition und Ernährung Deutsch med Wchnschr 53 517-519
48 SALKOWSKI E 1905 Zur Kenntnis der alkoholunloslichen, bzw kolloidalen Stickstoffsubstanzen im Harn Berl klin Wchnschr 42 1581 1583 1618 1620

51 ———— 1928 Concretions *In* Colloid Chemistry ed by J Alexander New York Chemical Catalog Co
52 SEIDELL, A 1919 Solubilities of Inorganic and Organic Compounds New York van Nostrand Co
53 TRÖLTZSCH J 1928 Eiweisssteine im Nierenbecken Ztschr f urol Chir 24 448-474
54 USUNI K 1929 Experimental studies on the influence of diet on the formation of biliary and renal calculi Japan J Gastroenterol 1 18, 1930 2, 276
55 VAN LEERSUM E C 1927 Vitamin A and urolithiasis Nederl Tijdschr v Geneesk 71 3370 3381
56 ———— 1927 Vitamin A deficiency and urolithiasis Brit Med J 2 873 874
57 ———— 1928 Vitamin A deficiency and urolithiasis J Biol Chem 76 13 142
58 ———— 1928 Vitamin A deficiency and calcification of epithelium of kidney Nederl Tijdschr v Geneesk 72 3077-3079
59 WEISER H B AND GRAY G B 1932 Colloidal phenomena in gall stones, J Phys Chem 36 286-299
60 ———— 1931 Mechanism of the formation of pure cholesterol gall stones Arch Path 17 1 9

PART III

BRIGHT S DISEASE AND VARIOUS OTHER PATHO LOGICAL RENAL CONDITIONS

CHAPTER XVIII

THE PATHOLOGY OF THE MAIN NEPHROPATHIES

BY E T BELL M D

DEGENERATIVE NEPHROPATHIES—NEPHROSES

NEPHROSIS is generally understood to include degenerative renal lesions in contradistinction from nephritis which designates inflammatory lesions The term *nephrosis* is not literally accur

and in many instances of nephrosis there are mild inflammatory reactions It is also uncertain whether thickening of the glomeru lar capillary basement membrane is an inflammatory or a degen *erative process For practical purposes it is probably better to* diagnose nephrosis when the lesion is *chiefly degenerative* and nephritis when it is *chiefly inflammatory* rather than to recognize mixed types

Degenerative
granular and fat

Inflammatory
interstitial tissues excessive accumulation of blood leukocytes in the glomerular capillaries or capsular spaces increase in the number and size of the glomerular capillary endothelial cells and increase in the number of cells in either the parietal or the visceral epithelial la*yer of Bowman s capsule*

There is some doubt as to the interpretation of changes in the capillary basement membrane The increase in thickness of this
rease of its substance
the recognized types
early not a hyaline
erprets it

All cases of nephrosis except the lipoid group are secondary to some o
en not prominent
If the
symptoms
clear u
nay result
in uremia Albuminuria and casts are often the only evidence of

renal injury but in special instances edema hypertension, anuria or renal insufficiency may develop

number of chemical poisons have been used to produce renal lesions Those most frequently employed for this purpose are uranium nitrate potassium bichromate mercuric chloride and racemic tartaric acid The lesion produced by a chemical poison is always a nephrosis never a nephritis

In clinical experience mercuric chloride nephrosis is about the only one of the chemical group that is encountered Persons that survive a day or longer after taking the poison develop anuria immediately or after a period of oliguria The urine shows albumin and casts There is a progressive rise of the blood metabolites There is no edema except a little in the face occasionally Hypertension develops in some instances during the period of anuria Death occurs in uremia In the event of recovery all evidence of renal disease finally disappears A chronic nephropathy does not develop

At postmortem the kidneys are slightly swollen and very cloudy Necrosis and disintegration of the cells of the convoluted tubules are outstanding histological features In those that die after several days calcified epithelial cells are frequently seen some of which are detached and others still connected with the basement membrane Newly formed epithelial cells begin to displace the necrotic ones after a few days

2 **Nephroses Due to Bacterial Poisons** —The majority of persons suffering from severe infectious diseases and infections show albumin and casts in the urine The infectious diseases which show albuminuria most frequently are lobar pneumonia diphtheria

sion

In f

cloudy

are usually somewhat enlarged and on section the cortices are always cloudy The cells of the convoluted tubules are swollen the cytoplasm often has a more vesicular structure and it may contain hyaline granules or fat droplets Necrosis is rarely seen but in unusually severe infections notably diphtheria necrotic tubules may be found (nephrotic nephrosis) The glomeruli appear normal in most instances but frequently especially in pneumococcic and streptococcic infections there is a distinct increase in the number and size of the capillary endothelial cells or an increase in the number

of polymorphonuclear leukocytes Sometimes the new cells in the capillaries are chiefly endothelial sometimes chiefly polymorphonuclear leukocytes Th — 1 f 1 of endothelial cells inflammatory reaction are not examples of a pure nephrosis as defined above They are really early stages of acute glomerulonephritis The glomerular lesions are fairly uniform and therefore cannot be interpreted as focal glomerulonephritis Such kidneys with mild glomerulitis cannot be distinguished clinically or macroscopically from those in which inflammatory changes are absent

3 **Nephroses Due to Jaundice** In severe obstructive jaundice albuminuria is often f d 1 f the obstruction In so frequent There thought that the renal injury is due to bile acids since these substances are said to increase in the blood after a short period of obstruction but to decrease after prolonged obstruction At postmortem the degree of cloudy swelling is obscured by the jaundice Microscopically minor degenerative changes are found in the tubules

Special Nephroses —This group includes special renal diseases which correspond more closely to nephrosis than to nephritis but which cannot be regarded as purely degenerative in character

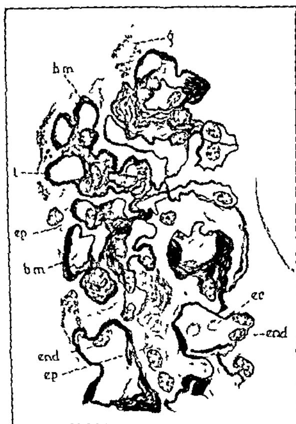
1 **The Nephrosis of Eclampsia** Eclampsia rarely develops before the fifth month of gestation Occasionally the first symptoms appear during or after labor The more prominent clinical features are albuminuria hypertension edema convulsions visual disturbances and headache Apparently no single symptom is absolutely essential in establishing the diagnosis There are a number of instances without convulsions reported in which hemorrhagic necrosis of the liver was found at postmortem

There is a retention of water and sodium chloride in eclampsia probably dependent upon extrarenal factors The non protein nitrogen of the blood is normal or slightly elevated Aside from the rare cases of cortical necrosis there is very little renal insufficiency

At postmortem the most characteristic lesions are found in the liver and kidneys In the liver one finds on macroscopic examination irregular areas of hemorrhagic necrosis in most instances but occasionally these lesions are not found

The kidneys are invariably swollen and on section the cortices are pale and cloudy The tubular epithelial cells are swollen and they may contain a number of small lipoid droplets The characteristic changes are found in the glomeruli In sections stained with hematoxylin and eosin it is noted that they are slightly enlarged and anemic On detailed examination it is found that the glomerular capillaries are very narrow and that this narrowing is

usually due to thickening of the capillary walls rather than to increase of endothelium In sections stained by the Mallory-Heidenhain technique it is seen that there is a very marked thickening of the capillary basement membrane (Fig 51) The thickened



[illegible] zo-carmine stain [illegible] erythrocyte [illegible] black end endothelial cell (Bell [illegible]

membrane causes narrowing of the capillary lumens Usually there is no increase of endothelial nuclei but in an occasional case the endothelial increase is a more prominent cause of capillary obstruction than thickening of the basement membrane The basement membrane shows a definite thickening in every instance but it is

more pronounced in some cases than in others Narrowing of the capillaries increases the resistance to the flow of blood through the kidneys and is probably the immediate cause of hypertension

In rare instances widespread cortical necroses are found in eclampsia

It is obvious that eclamptic kidneys with a definite increase of glomerular endothelium are not instances of pure nephrosis and one must interpret thickening of the basement *membrane as a* degenerative process in order to hold any eclamptic kidney in the group of nephroses

When a patient with chronic glomerulonephritis becomes preg nant there is usually an increase of the intensity of the nephritic symptoms *viz* albuminuria edema hypertension etc These cases of nephritis are apt to be confused with eclampsia unless the patient has been studied prior to the pregnancy or unless a definite renal insufficiency is present

The attack of eclampsia may leave some permanent damage in the kidneys In 1 of the author s cases in which the kidneys were studied seven years after eclampsia there were numerous hyaline glomeruli with atrophic tubules and other glomeruli with large fibrous areas in them

2 **The Amyloid Kidney** —Amyloid disease of the kidneys is usually associated with amyloidosis of other organs but rarely it occurs independently Clinically the renal lesion is usually over *shadowed by the major illness but in rare instances the* picture is predominantly one of renal disease The most frequent cause is tuberculosis with suppuration *viz* pulmonary tuberculosis with cavities and tuberculosis of the spine but a large variety of chronic suppurative processes may cause amyloidosis Occasionally no cause of the amyloid deposit can be found

[illegible] nt feat re

of

cie [illegible]

[illegible] of the serum proteins *The blood*

Amyloid

[illegible] nephrosis

a picture

of chronic uremia develops The blood pressure may become

[illegible] to [illegible] occurs

loid from

Amyloid is deposited chiefly in the glomeruli (Fig 52) It accumulates in the capillaries on the inner surface of the basement membrane never on its external surface When the deposit is small it is often possible to demonstrate the basement membrane

external to the amyloid, but sometimes the first deposit obliterates the membrane and when the capillaries are filled the membrane cannot be distinguished Any endothelial nuclei which may be present are pushed toward the lumen and enclosed in the amyloid mass The capillaries may remain permeable to the blood even after the glomerulus is greatly enlarged from amyloid infiltration but finally, they are obstructed completely and disuse atrophy of the tubule sets in The deposit of amyloid in the muscular coats of the small arteries and arterioles also tends to cut off the blood supply of the glomeruli Another factor in destruction of the



Fig 52 —Amyloid nephrosis Glomerulus showing a majority of its capillaries filled with amyloid Photomicrograph

tubules is plugging of their lumens with numerous large casts and occasionally also the deposit of amyloid under their basement membranes Amyloid is commonly deposited also in the walls of the vasa recta As a result chiefly of glomerular obstruction and casts renal insufficiency develops Amyloid kidneys with uremia may be contracted or large Hyaline granular degeneration of the tubules is frequent in amyloid disease

begins

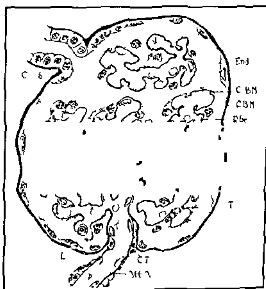
Lipoid nephrosis will be discussed under Glomerulonephritis

GLOMERULONEPHRITIS

Glomerulonephritis is defined broadly as a disease in which there are inflammatory changes of any kind in the glomeruli The evidences of an inflammatory reaction are swelling and prolifera tion of the capillary endothelium excessive accumulation of blood leukocytes in the glomerular capillaries and formation of intra capillary fibers The result of the various inflammatory reactions

it is of secondary importance

We distinguish a diffuse type in which practically all the glomer uli are involved and a focal type in which only a part of them are affected



Diffuse Glomerulonephritis —In order to give a clear presentation

basement membrane, which is covered externally by the glomerular epithelium and lined internally by endothelial cells There are relatively few endothelial nuclei The great majority of the nuclei in a normal glomerular tuft belong to the epithelial cells The endothelial cells apparently do not form a continuous layer The capillary basement membrane is continuous with the capsular basement membrane which is an extension of the basement membrane of the convoluted tubule The proper staining of the capillary basement membrane is essential in the study of the finer histology of glomerular lesions



Fig 54 —Acute exudative glomerulonephritis non-clinical type From a case of lobar pneumonia Note large number of polymorphonuclear leukocytes within the capillaries Drawing

1 **The Non-clinical Type** —The non-clinical type is found frequently if one makes a routine microscopic study of kidneys from persons dead of infectious processes The clinical picture is that of a nephrosis secondary to bacterial infection The characteristic clinical findings of glomerulonephritis, *viz*, edema hypertension, etc, are absent In the author's experience, puerperal sepsis, lobar pneumonia and streptococcic bacteriemia most frequently give rise to this lesion

At postmortem the kidneys show a marked degree of cloudy swelling The tubular epithelium is swollen and may contain hyaline-granular and fat droplets The glomeruli all show an increase of nuclei On detailed study the capillaries are found to contain an increased number of endothelial cells or polymorpho-

nuclear leukocytes It is clear that the polymorphonuclear leukocytes are derived from the blood and when these cells predominate as shown in Fig 54 we may speak appropriately of exudative glomerulonephritis But often the cells in the capillaries are all endothelial and it is clear that we are dealing with an early stage of acute diffuse proliferative glomerulonephritis (Fig 55) The capillaries are only partially obstructed and there are no intracapillary fibers as in clinical glomerulonephritis (see below)

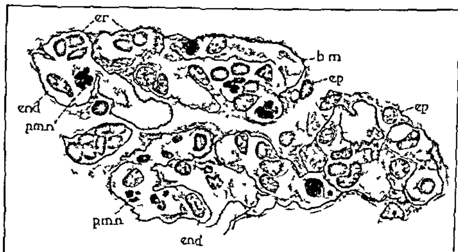


Fig 55 Early acute diffuse glomerulonephritis (non-clinical) From a case of lobar pneumonia Azo-carmine stain Drawing under high magnification *b m* Capillary basement membrane *end* endothelial cell *ep* glomerular epithelial cell *er* erythrocyte *p m n* polymorphonuclear leukocyte

2 **Typical Clinical Glomerulonephritis** —This may be subdivided according to the clinical course into acute subacute and chronic A clinical distinction between these three groups is useful but somewhat arbitrary Pathologically the lesions in the three groups differ markedly in degree and extent but very little in quality There are numerous transition cases between the groups both clinically and pathologically

(*a*) *Acute Glomerulonephritis* —Acute glomerulonephritis practically always follows an acute infectious process of some kind The infections most frequently giving rise to glomerulonephritis are sore throat and scarlet fever but many other infections are occasionally responsible *viz* infected wounds otitis media empyema peritonitis etc The symptoms of renal involvement commonly appear from one to three weeks after the onset of scarlet fever and a few days after a sore throat The association of acute glomerulo-

nephritis with streptococcic and pneumococcic infections is so impressive that very few investigators doubt the causative relationship of these organisms to the disease

The clinical symptoms vary with the severity of the disease In

duration or entirely absent The diagnosis may be made on the presence of edema albuminuria and erythrocytes in the urine In the absence of both edema and hypertension the diagnosis cannot be established

20 to 40 mm Hg during the first few days but it is often found normal in mild cases after this period In severe cases hypertension is seldom absent Oliguria is frequent and anuria may occur

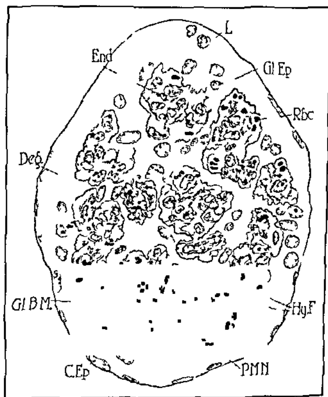
The majority of patients with acute glomerulonephritis pass through the acute stage within a few months A few die of uremia after an acute or subacute course and a great many pass on into an active or latent chronic stage The majority of children recover completely but it is believed that about 50 per cent of adults ultimately develop a chronic nephritis after a latent stage of many years duration Many of the soldiers who had acute nephritis during the World War and were thought to have recovered finally developed chronic nephritis after a latent period of from five to ten years

Macroscopically in the acute stage the kidneys are enlarged and cloudy The external surfaces are smooth There are no certain gross distinctions from a nephrosis but glomerular hemorrhages are suggestive of nephritis

Microscopic sections under low magnification show enlarged avascular glomeruli with an increased number of nuclei The diameter of the glomerulus is often increased as much as 50 per cent There is an enormous increase in the number of nuclei With ordinary stains that do not bring out the capillary basement membrane it is very difficult to determine the source of the new cells but when this membrane is stained as may be done with Heidenhain s modification of Mallory s aniline blue stain it is seen that nearly all the new cells lie within the membrane In Fig 56 which illustrates an early stage of acute glomerulonephritis the detailed structure is shown The glomerular epithelial cells have not increased and correspond with the normal except for a slight increase in size There are only a few erythrocytes in the capillaries the lumens being filled mainly with mononuclear cells The mononuclear cells are for the most part attached to the capillary

walls and are interpreted as endothelial in origin but it is possible that some of them are mononuclear leukocytes from the blood They fuse to form syncytial masses which distend the capillaries and leave little or no space for the erythrocytes

A variable number of polymorphonuclear leukocytes are seen in the capillaries *Sometimes they are numerous but usually there* are only a few as in Fig 56 They are surrounded by endothelial cells and they usually show evidences of degeneration



A prominent feature is the presence of numerous hyaline fibers which form a meshwork about the endothelial cells and leukocytes The nature of these fibers has not been determined They stain similarly to the capillary basement membrane and show numerous connections with it They do not give the staining reactions of

fibrin When first formed they do not give the staining reactions of collagen, but later on they stain like collagenous fibers The increase in the number and size of these fibers is responsible for the hyaline appearance of the glomerulus in the later stages

As the lesion becomes chronic, the intracapillary fibers increase

bare nuclei are left surrounded by hyaline material



Fig 57 —Glomerular capillary loops from a case of chronic glomerulonephritis *Azo-carmine stain The capillaries are enlarged and filled with endothelial cells and* intracapillary fibers. (Drawing) *b m* Basement membrane *end* endothelial nuclei *ep* epithelial cells *f* network of intracapillary fibers (Bell's Text-book of Pathology)

The fundamental change in glomerulonephritis is, therefore, occlusion of the capillaries by the growth of the endothelial cells, the formation of intracapillary fibers and the accumulation of leukocytes These processes may be called intracapillary glomerulonephritis

The capsular epithelium sometimes proliferates extensively to form crescent-shaped masses which compress the glomerular tuft (Fig 58) These are called epithelial crescents, and they are more frequently seen in fulminating cases This process may be called extracapillary glomerulonephritis The glomerular epithelium, *i e*,

the visceral layer, does not take an active part in the reaction The pressure of an epithelial crescent may be the main cause of occlusion of the glomerular capillaries, but an intracapillary glomerulitis is always present

One of the features of clinical acute glomerulonephritis is that it is diffuse, and it is commonly stated that every glomerulus is injured *However, a thorough study of the kidneys in acute cases will usually* reveal some glomeruli in which there is very little capillary obstruction It is easily determined that the capillary occlusion is extreme in some and only moderate in others Apparently every glomer-

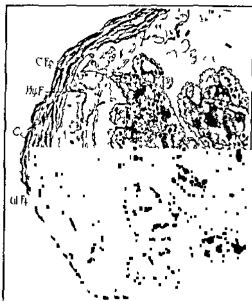


FIG 58 —Chronic diffuse glomerulonephritis Stain as in Fig 56 Drawing by Leone McGregor Lettered as in Fig 56 The intracapillary fibers have fused to form solid hyaline masses (*Hy*) enclosing the endothelial nuclei Some of the glomerular capillaries are permeable An epithelial crescent is shown (C)

ulus is injured but the degree of injury as represented by closed capillaries, is variable [illegible] the

[illegible]

subacute stage

Apparently no study has been made of the glomerular lesions in cases of acute glomerulonephritis that terminate in recovery The

author has had the opportunity of studying one atypical case. This was a male child aged twenty-one months who had been suffering from otitis media for six weeks before admission. There was a purulent discharge from both ears. The temperature ranged from normal to 100° F. The leukocyte count varied from 16 000 to 37 000—the differential count showed 70 to 84 per cent polymorphonuclears. There was a trace of albumin in the urine and on one occasion numerous erythrocytes. There were many leukocytes in the urinary sediment. There was no edema. No blood pressure was recorded. One kidney was removed under an erroneous diagnosis of abscess or tumor. This is not a clinical picture of acute diffuse glomerulonephritis but one which would be interpreted as focal nephritis. The kidney was cloudy and swollen. There was no pyelitis. The glomeruli are all involved. They are very cellular and anemic. There is a marked increase of endothelial cells in most of the capillaries and some capillaries are completely closed by endothelial cells and intracapillary fibers. However the majority of the glomerular capillaries are patent. There are a few epithelial crescents. The child has subsequently recovered completely.

Notwithstanding the atypical clinical picture this case can only be interpreted as acute diffuse glomerulonephritis of mild degree. If we accept this case as representative of mild acute diffuse glomerulonephritis it is clear that recovery comes about because relatively few capillaries are completely closed.

The tubular epithelium in acute glomerulonephritis is always injured to some extent but the functional disturbance is clearly due largely to obstruction of the glomerular circulation.

Often there is an exudate of leukocytes in the interstitial tissues about the glomeruli. Leukocytes and erythrocytes escape from the glomerular capillaries and enter the lumina of the tubules where they are often seen in large numbers. Hemorrhage occurs chiefly from glomeruli that have patent capillaries and are therefore much less damaged than occluded glomeruli that cannot bleed.

Acute glomerulonephritis occurred in epidemic form during the World War among the soldiers especially those in the trenches. It has been referred to as war or trench nephritis. There are no anatomical differences between war nephritis and acute glomerulonephritis as described above.

(b) Subacute Glomerulonephritis. This group blends on the one side with the acute and on the other side with the chronic type. Subacute may be properly applied clinically to a case that terminates in uremia after a duration of several months. The typical clinical picture is heavy albuminuria with casts and erythrocytes, marked edema, marked hypertension and progressive renal insufficiency.

At postmortem the kidneys are found enlarged and cloudy The external surfaces are smooth and the cortices are somewhat increased in thickness Microscopically the tubules all show a pronounced atrophy but very few have disappeared entirely (Fig 59) The glomeruli are enlarged and bloodless The capillaries are completely occluded by swollen endothelial cells intracapillary fibers and leukocytes Epithelial crescents are usually numerous There are relatively few hyaline glomeruli Lesions of this type probably begin as a severe injury to nearly all the glomeruli The closure of the *glomerular capillaries brings about a slow disuse*

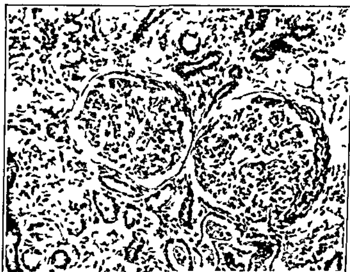


Fig 59 —Subacute glomerulonephritis The glomeruli are enlarged and their capillaries are almost completely closed The tubules show a rather marked atrophy This appearance is found in all parts of the kidneys There is no gross contraction of the kidneys (Photomicrograph from Bell s Text-book of Pathology)

atrophy of the tubules and a progressive failure of renal function There is extensive tubular atrophy but the kidneys do not have sufficient time to contract as they do in chronic cases

(c) *Chronic Glomerulonephritis* —This is a disease of slow development and long duration The early stages are not well known since the patient seldom comes to our attention until the disease is far advanced Only a few cases give a history of a definite clinical acute glomerulonephritis but it is nevertheless probable that at least a mild acute onset has occurred some years previously The usual initial symptoms are weakness dyspnea on exertion headache hypertension edema of the ankles and albuminuria The disease

is commonly present a long time before any definite symptoms develop.

Some cases are discovered at a relatively early stage in the course of a routine examination for life insurance or other purposes. In these latent cases the symptoms and signs are less pronounced than in the active chronic case. There may be little or no edema, the blood-pressure is only slightly elevated or normal and anemia is not severe. Persistent albuminuria and casts call attention to the renal lesion.

The course of chronic glomerulonephritis is usually characterized by exacerbations and remissions. The exacerbations are brought on by colds, sore throat and other infections and result in aggravation of all the symptoms. During the remissions the patient improves, sometimes to the point of complete disappearance of albuminuria. Renal function becomes progressively poorer in the course of the disease.

Albuminuria and casts are always present except in rare instances during remissions in mild cases.

Edema is variable. It is usually more pronounced during acute exacerbations and it is often absent over long periods. There is no definite relation between the amount of edema and the degree of renal insufficiency. Cases in which edema is prominent are often spoken of as the "parenchymatous" or "nephrotic" type. Edema is influenced by the severity of albuminuria, the fluid intake, rest in bed, the type of glomerular lesions and unknown factors.

Hypertension is nearly always present but may be absent in mild cases. The systolic blood pressure usually ranges between 140 and 180 mm. Hg. It is not often above 200 mm. Hg, but cases of many years' duration in which a marked arteriolosclerosis has developed may have pressures above 200 mm. Hg.

Renal function is not markedly impaired until extensive occlusion of the glomerular circulation has developed. Blood-urea nitrogen is normal or only moderately elevated until the final stage of the disease is reached. The excretion of phenolsulphonephthalein is definitely reduced before there is a convincing rise of blood urea nitrogen.

Secondary anemia develops along with renal insufficiency.

In many cases of chronic glomerulonephritis, as well as in some acute and subacute cases, there is a decrease of plasma proteins, especially serum albumin, and an increase of blood lipoids. These phenomena are usually more pronounced when edema is present. A decrease of plasma proteins may be found in other types of renal disease, e.g., lipoid nephrosis, amyloid nephrosis, nephrosis of pregnancy and sublimate nephrosis. It may also occur in diseases of extrarenal origin, particularly lobar pneumonia and famine edema.

The decrease of plasma proteins may develop in the complete absence of edema as in lobar pneumonia However, a severe edema is usually associated with low serum proteins, and when the serum albumin falls as low as 0 8 per cent, edema is almost invariably present

Macroscopic Appearance —The kidneys in chronic glomerulonephritis are of two types contracted and non-contracted The latter belong to the lipoid nephrosis group, which will be discussed in a subsequent paragraph The contracted kidneys together usually weigh from 100 to 200 gm Some are much smaller than others In general, the smaller kidneys are found in the cases of longer duration The capsules are adherent firmly, and the external surfaces are finely pitted There are no cortical denomas as in the hypertenve kidneys On section the rtices are much thinner than rmally and indistinctly de- rcated from the pyramids cortices usually have a owish tinge—a feature of t value in distinguishing erulonephritis from hy- nsive contracted kidneys



racted kidney onic glomerulonephritis with the hyaline glomeruli The tubules associated disappeared The large glomeruli have practically histological structure similar to those shown in Figs 57 and 58 The tubules associated with the large glomeruli are fatty Photo- micrograph

roscopic Structure — A large percentage of the glomeruli are hyaline (Fig 60), in some instances as high as 90 per cent The tubules associated with such glomeruli have either disappeared entirely or they are represented by small epithelial cords The areas previously occupied by tubules are shrunken and contracted, and the surface of the kidney over such areas is depressed, giving the pitted appearance The increase of fibrous tissue in the atrophic areas is largely relative

The tubules that have not undergone atrophy are associated with glomeruli that are enlarged but not hyaline (Fig 60) These glomeruli show an increase of capillary endothelium but the capillaries are not completely obstructed (Figs 57 and 58) In the final stages of chronic glomerulonephritis the few glomeruli that persist show partial occlusion of their capillary circulation The

persistent convoluted tubules are dilated and show a variable amount of fat in their cells

Pathogenesis —As stated above only an occasional case of chronic glomerulonephritis begins as a typical acute clinical case In the vast majority the immediate inciting cause is unknown The most convincing evidence that the disease is inflammatory in origin is the histological structure of the glomerular lesions The

morphonuclear leukocytes are also found imprisoned in the closed capillaries Epithelial crescents are seen frequently The chief difference between acute and chronic stages is due to increase and fusion of intracapillary fibers

The atrophy of the tubules is closely related with the occlusion of the glomerular capillaries It is clearly a disuse atrophy and not the result of anemia The capillaries among the tubules anastomose freely and open capillaries are regularly seen between atrophic tubules

The Arterioles —The afferent glomerular arterioles frequently *show small areas of hyaline degeneration in acute and subacute* cases and in occasional chronic cases of many years duration a high degree of arteriolosclerosis may be found In such instances a clinical distinction from primary hypertension can hardly be made but a careful microscopic study will disclose the character of the lesion

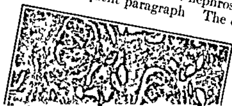
Subgroup Lipoid Nephrosis Lipoid nephrosis is not a new disease In the older literature it was known as parenchymatous nephritis It was brought to our attention by Volhard and Fahr in 1914 as genuine nephrosis Epstein in his extensive studies on this disease referred to it as chronic nephrosis The term lipoid nephrosis suggested by Munk has apparently supplanted the other terms in the current literature

The clinical features of a typical case of pure lipoid nephrosis are the presence of severe albuminuria with casts oliguria marked edema hypercholesterolemia and decrease of the plasma proteins

enumerated above become less prominent Published reports indicate that about 50 per cent recover ultimately, although albuminuria may persist for several years About one-half of the

The decrease of plasma proteins may develop in the complete absence of edema as in lobar pneumonia. However, a severe edema is usually associated with low serum proteins, and when the serum albumin falls as low as 0.8 per cent, edema is almost invariably present.

Macroscopic Appearance.—The kidneys in chronic glomerulonephritis are of two types, contracted and non-contracted. The latter belong to the lipoid nephrosis group which will be discussed in a subsequent paragraph. The contracted kidneys together usually weigh from 100 to 200 gm. Some are much smaller than others. In general, the smaller kidneys are found in the cases of longer duration. The capsules are adherent firmly, and the external surfaces are finely pitted. There are no cortical adenomas as in the hypertensive kidneys. On section the cortices are much thinner than ormally and indistinctly de-arcated from the pyramids. he cortices usually have a llowish tinge—a feature of at value in distinguishing merulonephritis from hy-ensive contracted kidneys.



...ronic glomerulonephritis ...racted kidney. The tubules associated with the hyaline glomeruli have practically disappeared. The large glomeruli have a histological structure similar to those shown in Figs. 57 and 58. The tubules associated with the large glomeruli are fatty. Photomicrograph.

icroscopic Structure.—A large percentage of the glomeruli are hyaline (Fig. 60), in some instances as high as 90 per cent. The tubules associated with such glomeruli have either disappeared entirely or they are represented by small epithelial cords. The areas previously occupied by tubules are shrunken and contracted, and the surface of the kidney over such areas is depressed, giving the pitted appearance. The increase of fibrous tissue in the atrophic areas is largely relative.

The tubules that have not undergone atrophy are associated with glomeruli that are enlarged but not hyaline (Fig. 60). These glomeruli show an increase of capillary endothelium, but the capillaries are not completely obstructed (Figs. 57 and 58). In the final stages of chronic glomerulonephritis the few glomeruli that persist show partial occlusion of their capillary circulation. The

persistent convoluted tubules are dilated and show a variable amount of fat in their cells

Pathogenesis — As stated above only an occasional case of chronic glomerulonephritis begins as a typical acute clinical case In the vast majority the immediate inciting cause is unknown The most convincing evidence that the disease is inflammatory in origin is the histological structure of the glomerular lesions The lesions can only be interpreted as the outcome of acute glomerulitis A comparison of the acute stage shown in Fig 56 with the chronic stages shown in Figs 57 and 58 brings out this relation In the chronic stage the endothelial cells are still prominent but they are *compressed by a great increase in the intracapillary fibers* Polymorphonuclear leukocytes are also found imprisoned in the closed capillaries Epithelial crescents are seen frequently The chief difference between acute and chronic stages is due to increase and fusion of intracapillary fibers

The atrophy of the tubules is closely related with the occlusion of the glomerular capillaries It is clearly a disuse atrophy and not the result of anemia The capillaries among the tubules *anastomose freely and open capillaries are regularly seen between* atrophic tubules

The Arterioles The afferent glomerular arterioles frequently show small areas of hyaline degeneration in acute and subacute cases and in occasional chronic cases of many years duration a *high degree of arteriolosclerosis may be found* In such instances a clinical distinction from primary hypertension can hardly be made but *a careful microscopic study will disclose the character* of the lesion

Subgroup Lipoid Nephrosis Lipoid nephrosis is not a new disease In the older literature it was known as parenchymatous nephritis It was brought to our attention by Volhard and Fahr in 1914 as genuine nephrosis Epstein in his extensive studies on this disease referred to it as chronic nephrosis The term lipoid nephrosis suggested by Munk has apparently supplanted the other terms in the current literature

The clinical features of a typical case of pure lipoid nephrosis are the presence of severe albuminuria with casts oliguria marked edema *hypercholesterolemia and decrease of the plasma proteins*

indicate that about 50 per cent recover ultimately although albuminuria may persist for several years About one-half of the

deaths are due to peritonitis and the rest to other infections Uremia does not develop

Pure lipoid nephrosis is usually defined anatomically as follows The enlarged kidneys show smooth external surfaces and thickened *cortices of light yellowish color* *Microscopically* the tubular epithelium contains a variable number of lipoid droplets and the glomeruli are practically normal

Nearly all observers describe the *glomeruli as normal or practically normal* and it is this feature which is believed to distinguish lipoid nephrosis from chronic glomerulonephritis

The idea that the glomeruli are normal has given rise to the widespread opinion that lipoid nephrosis is not a primary disease of the kidney but a general metabolic disorder with secondary renal changes

If rigid clinical criteria are applied and no cases are included which show any elevation of blood pressure or evidence of renal insufficiency lipoid nephrosis in adults becomes a very rare disease However one *frequently* sees *cases which* correspond to *lipoid*

hypertension or

nephritis with

re thoroughly a

nephrosis is studied the more frequently it is found to correspond with the mixed type In children the clinical picture of pure lipoid nephrosis is not especially rare Occasionally a disease that appears to be a pure nephrosis later becomes a definite glomerulonephritis

A microscopic section of a *pure lipoid nephrosis* is shown in Fig 61 Under low magnification the glomerulus does not appear markedly abnormal but under high magnification it is seen that the capillaries are partially obstructed by new cells The extent

... appreciated when special

with endothelial cells * The newly formed endothelial cells are so filled with lipoid droplets that they are barely visible in routine preparations In another case of pure lipoid nephrosis described in the paper just referred to there was partial obstruction of some *of the capillaries* by endothelial cells and an uneven thickening of the capillary basement membrane

In many cases reported *in the literature in which the glomeruli* are described as normal it appears probable from the accompanying illustrations that definite glomerular alterations could have been demonstrated with appropriate technique Fahr[6] in his latest pub-

* See Am J Path vol 5 Plate 105 Fig ? 1929

lication on nephrosis illustrates hyaline thickenings of the walls of the capillaries But it must be admitted that instances of lipoid nephrosis occur in which the glomerular alterations are minimal e g Amberg s case and one of Klemperer s cases Even when no structural changes are demonstrable there must however be an

followed by endothelial reaction and resulting capillary obstruction the clinical picture is that of nephritis but in the absence of reaction or with incomplete capillary obstruction the resulting clinical picture is nephrosis This interpretation gives a simpler explanation of the mixed type than the assumption that we are dealing with two diseases ie nephrosis and nephritis mixed in varying proportions It also affords an easy explanation for the observation that a nephrosis frequently passes over into a nephritis—the capillary obstruction becomes more pronounced



FIG 61 Pure lipoid nephrosis Low magnification The tubules are somewhat dilated and they show many lipoid droplets in the cytoplasm The glomeruli show some capillary obstruction Photomicrograph

The nephroses of mixed type (nephritis with nephrotic tendency) all show pronounced glomerular changes The kidneys are not contracted The tubules show a moderate degree of atrophy as is indicated by the increased space between them and there are numerous lipoid droplets in the cytoplasm In the glomeruli there is sometimes an endothelial increase with intracapillary fibers as in typical glomerulonephritis but more often the structure is such as is shown in Fig 62 The walls of the capillaries are thicker and their lumens are narrowed With the Mallory Heidenhain stain it can be seen that the narrowing of the capillaries is largely due to massive thickening of the capillary basement membrane *

* See Am J Path vol 5 Plate 108 Figs 4 and 6 1929

In cases of lipoid nephrosis of mixed type that terminate in uremia the glomerular capillaries are gradually obliterated by thickening of the basement membrane the glomerulus is no longer permeable to blood and the tubule undergoes atrophy A fairly advanced stage of this process is shown in Fig 63 It is surprising that thickening of the capillary basement membrane is associated with increased permeability to proteins but very high magnification of thickened membranes discloses numerous irregular spaces in their substance in fact thickened membranes have a porous structure which cannot be seen in the normal membrane

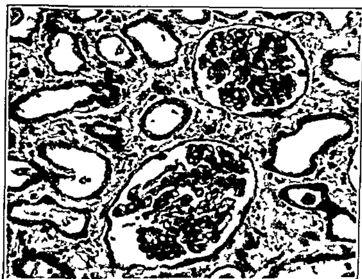


Fig 6? —Nephrit s with neph otic tendency Low magn ficat on Stained with iron hematoxylin The glomerular capillar es are narrow and many are com pletely closed The tubules are dilated and show an early stage of atrophy (Photo m crograph from Bell s Text-book of Pathology)

The mixed type of lipoid nephrosis is described under various names ii hydropic type of glomerulonephritis nephrotic type of glomerulonephritis and parenchymatous nephritis The kidneys differ macroscopically from those of the azotemic or ordinary type of glomerulonephritis in that they are large and fatty and not contracted as in the latter Microscopically the glomerular capillaries in the nephrotic type are narrowed but not completely obstructed and tubular atrophy is therefore not pronounced The narrowing of the capillaries is brought about in most instances by thickening of the basement membrane but endothelial increase is often a minor and sometimes a major factor The open capillaries with their porous membranes allow the continuous escape of serum

proteins in the urine with resulting edema and hypercholesterolemia It is therefore this structural difference in the glomerular lesions which brings about the clinical differences between hydropic and azotemic glomerulonephritis

It does not clarify our conception of this renal lesion to regard it as a mixture of two diseases [illegible] nephrosis and nephritis It may be interpreted more simply as a form of glomerulonephritis with alteration of the capillary walls but incomplete capillary obstruction

The pure type of lipoid nephrosis is interpreted as injury of the glomerular capillaries with less pronounced structural changes There are so many transitions between the pure and mixed types both clinically and anatomically that it is hardly possible to interpret the pure type as a distinct entity



inflammatory process

Neither the clinical nor the pathological conception of this type

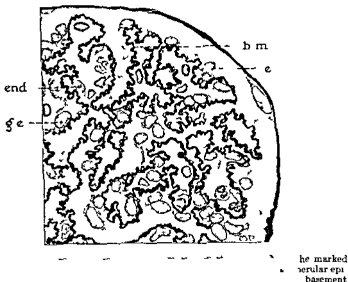
ular external surfaces and in the remainder there is more or less decrease in size with granular surfaces In only about 15 per cent is there sufficient atrophy to warrant the term contracted kidney The term primary contracted kidney is used somewhat arbitrarily to designate hypertensive kidneys that show a high degree of atrophy

On microscopic examination 90 per cent of the kidneys from cases of primary hypertension show sclerosis of the afferent glomerular arterioles The small arteries immediately preceding these arterioles are diseased in 98 per cent but disease of these vessels occurs also in non hypertensive cases In 10 per cent the disease has not extended into the afferent glomerular arterioles



Fig 64 —Arteriolosclerotic kidney Longitudinal section of an afferent glomerular arteriole showing a subintimal deposit of hyaline Photomicrograph

In arteriolosclerosis the structural changes consist in a subintimal deposit of a hyaline material (Fig 64) The hyaline is deposited in a layer of uneven thickness As it increases in amount it tends to cause atrophy of the muscular layer and narrowing of the lumen The hyaline deposit sometimes extends out into the tuft The first change observed in the glomerulus is a thickening and wrinkling of the capillary basement membrane (Fig 65) The arteriolar lesion precedes that in the glomerulus As the arteriole becomes narrowed the glomerular capillaries collapse and the basement membrane increases until the entire glomerulus assumes a compact,



he marked
ıerular epı
basement



FIG 66 Small renal artery in primary hypertension Elastic tissue stain Note the marked thickening of the intima due to increase of elastic tissue and the atrophy of the media

shrinks and the surface of the kidney becomes pitted Renal insufficiency develops when the atrophy becomes pronounced Sclerosis of small arteries is as important as arteriolosclerosis in causing atrophy and renal insufficiency

Sclerosis of small arteries consists *mainly in a great increase of* elastic tissue in the intima (Fig 66) This is called hyperplastic elastic intimal thickening It is interpreted as a compensatory phenomenon resulting from increased intravascular pressure The media of these arteries undergoes atrophy

Hypertension With Uremia —Approximately 10 per cent of the deaths from primary hypertension are due to uremia The usual *case is a chronic hypertension with slowly developing uremia* In this type uremia is due to a gradual occlusion of small arteries and arterioles In about one-fourth of the cases, uremia develops

uremias a number of glomeruli show acute glomerulitis This has been *regarded as distinctive of uremic hypertension (Fahr)*, but McGregor found occasional glomeruli of this type in all forms of hypertension

[illegible] "malignant hypertension" to denote [illegible] changes [illegible] rtension

By no means all cases of hypertension with uremia [illegible] minating in type The expression fulminant hypertension" seems more appropriate to designate hypertension with rapid development of uremia Acute uremia in the course of hypertension may be due to a superimposed infection

It is believed that primary hypertension begins as a *generalized* spasm of arterioles The existence of arteriolar spasm is readily demonstrated in early cases by the fall of blood pressure which occurs during sleep and under the influence of amyl nitrite In the more advanced types this relaxation cannot be brought about It [illegible] sulting from [illegible] which we [illegible] cur readily [illegible] developed

This hypothesis does not explain the intensity of arteriolosclerosis in the kidneys and its usual absence in many regions, notably the skin and the muscles On the other hand, if we adopt the theory that arteriolosclerosis of the kidney is the primary lesion and that

hypertension is of reflex origin we are unable to explain those cases without renal arteriolosclerosis

It is important to distinguish chronic glomerulonephritis from primary hypertension with uremia whenever possible since the two diseases are entirely different in etiology Clinically chronic glomerulonephritis shows moderate cardiac hypertrophy and hypertension edema albuminuria secondary anemia and a slowly developing uremia Cardiac decompensation is rare Cases of many years duration may develop very high blood pressure extensive arteriolosclerosis and retinitis This type can hardly be distinguished clinically from primary hypertension At postmortem the kidneys show granular surfaces but small subcapsular adenomas are unusual On section the cortices are yellowish Microscopically there are evidences of old glomerulitis which are readily recognizable unless arteriolosclerosis is extreme

Primary hypertension is readily distinguished clinically from chronic glomerulonephritis except in the cases which develop renal insufficiency These may present some difficulty Primary hypertension is suggested if there is at any time definite evidence of cardiac failure apoplexy or coronary disease The eyegrounds are usually characteristic Marked enlargement of the heart and very high blood pressure also indicate primary hypertension

REFERENCES

1 BELL, E T 1929 Lipoid nephrosis Am J Path 5 587–622
2 ——— 1932 Renal lesions in the toxemias of pregnancy Am J Path 8 1–40
3 ——— 1932 Glomerular lesions associated with endocarditis, Am J Path 8 639–664
4 ——— 1932 Relation of lipoid nephrosis to nephritis, Ann Int Med 6 167 182
5 BELL, E T AND CLAWSON B J 1928 Primary hypertension Arch Path 5 939–1002
6 FAHR TH 1925 Handbuch der speziellen pathologischen Anatomie und Histologie 6 Pt 1
7 MCGREGOR L 1929 The finer histology of the normal glomerulus The cytological changes occurring in the glomerulus of clinical glomerulonephritis, Am J Path 5 545–585
8 ——— 1930 Histological changes in the renal glomerulus in essential (primary) hypertension Am J Path 6 347 366

CHAPTER XIX

CONGENITAL RENAL ANOMALIES

By STANLEY P REIMANN M D

Introduction Factors Responsible for Renal Anomalies —Congenital anomalies are usually explained on the basis of the normal developmental course of the kidney and ureter This presupposes a definite and settled knowledge of their embryology otherwise controversies in the latter will be carried over into the former At the present time however it is not sufficient merely to describe these deviations from the normal in anatomical terms and relate them to anatomical embryological considerations for during the past decade there have accumulated data in genetics and experimental embryology or as it is sometimes called developmental mechanics which allow the introduction of physiological concepts and even a few chemical terms

The possibilities are overwhelmingly in favor of the view that the structural elements which transmit species specificity as well as individual peculiarities are contained mostly within the chromosomes But the cytoplasm also is not to be neglected in this consideration The probabilities are that the human ovum is at least partially regulatory which means that slight defects acquired before or shortly after fertilization do not determine a defective adult In other words the ovum can regulate or compensate for and overcome some defects with the ultimate production of a perfect individual In this process and in normal development also the phenomena of organizers as discovered and elaborated particularly by Spemann and his school can be applied to the kidney as well as to other organs

Briefly the organizer phenomena are as follows In the segmenting ovum but little differentiation of the oncoming cells is discern

hand are divided absolutely equally between all cells In developing embryos of such animals as sea urchins tritons etc which can be observed readily a few cells may be seen then in a region called the dorsal lip When these cells appear a profound change

takes place in the whole embryo cell division is retarded and differentiation and organization receive a great impetus The embryo soon takes on definite structure and begins to look like something Then cell proliferation is again accelerated whereupon the previously differentiated parts in their turn act as organizers and guide the newly produced cells into the channels proper for the particular time and of course kind of embryo The new cells being differentiated act as organizers on their own account and so on

Probably the embryo has now reached a size where simple contact and diffusion are inadequate for communication between cells and for regulating and integrating their activities hence nerves are developed which flash messages to and fro and thus govern the growth as a whole Later genuine ductless glands are added as cells are differentiated for their production and these also act as coordinators All these factors together plus the developing and organizing influence of function as it is begun by tissues as well as doubtless many other factors lead the growth into the proper differential relations so that a liver does not grow too big for the heart the heart remains the proper size for the lungs etc Furthermore the structures are also developed in tune with those of the lineage from which the embryo arose

All through this process the chromosomes act as guides and probably also as restrainers That is living protoplasm is capable of infinite variation the chromosomes restraining this unlimited potency and forcing the organism to remain species specific and individual Hence in any comprehensive study of kidney anomalies we must consider chromosomes cytoplasm organizers and other guides such as nerves bloodvessels probably enzymes hormones and many other chemical substances

If the chromosomes determine congenital anomalies then they should be hereditary in every sense of the word and should behave in succeeding generations according to Mendel s laws That certain anomalies are produced by these means is attested by human hereditary studies wherein such things as horseshoe and polycystic kidneys have been shown to occur in numerous members of a family

When trouble arises in the cytoplasm as a cause of congenital anomalies modern genetics says this also can be hereditary (Little[17]) On the other hand it is easier to imagine acquired defects in the cytoplasm than in the chromosomes Acquired changes in chromosomes are called mutations and the possibility of a mutation occurring in a fertilized ovum coming from healthy parents cannot be overlooked as another cause of kidney anomalies

Trouble from organizers nerves chemicals etc are more probably acquired And even though we know little of the details of

such troubles nevertheless Stockard for instance has obtained congenital anomalies by varying the oxygen tension Other workers report the production of various abnormalities even monstrosi

SPECIFIC EXAMPLES OF CONGENITAL RENAL ANOMALIES

The first to be discussed is naturally the anatomy of embryonic development Two ideas one of which has been almost discarded are current in respect to the subject The one most generally believed is that the kidney and ureter are developed from two separate anlagen the cortex *i e* glomeruli and tubules to collecting tubules from one (the so-called renal blastema) and the pelvis of the ureter and collecting tubules from the other (the ureric bud which arises after the union of the Wolffian duct and the cloaca) The two developing structures meet and junct on is effected so nvoluted tubules Henle come into thus producing a continuous system from glomerulus to pelvis Failure of proper union of a few or many results in the common congenital anomaly of cystic kidney with many or few cysts accompanied by a corresponding reduction in the number of tubule systems in working order The practical aspect consists almost entirely in how many *of these tubule systems are workable that is again a question* of kidney function in respect to the number of active units

Occasionally a polycystic kidney may be large enough or even be displaced so as to produce pressure on neighboring organs such gall bladder bile ducts colon etc The matter of pressure of the cysts on what normal kidney tissue exists is also no doubt of utmost importance the maintenance of life depending on preserving the integrity of what tubule systems are present Such individuals also should be protected more than ordinarily against colds infection etc and in woman extra care during pregnancy both because of the additional physiological strain and because of pressure from the growing uterus

When either the renal blastem hindered from developing no ki Boyden[2] beleves that failure of of the ureter (three fourths of cases) and seldom if ever of the renal blastema itself

Thus for the production of kidney anomalies are obtained anatomical explanations from the embryology Since they

appear in standard textbooks they will be alluded to here only
the wealth of knowledge
e mode of production of
is still obscure As an
example may be cited the discussion of Boyden[1] of the role of the
circulation in horseshoe kidney i e whether the anomaly itself
organized vessels not ordinarily appearing in ontogeny or whether

theories which have been advanced for their formation—those
dealing with extrinsic causes and those that attribute fusion to
deviations that are inherent in the primordia of the kidneys He
illustrates the second group by the theory that two ureters may

bifurcation of the aorta into umbilical or common iliac arteries
This bifurcation forms a U shaped crotch in which the kidneys are
lodged and from which they escape by migrating upward The
arteries as a mechanical obstruction tend to bring the right and

the lower poles in which case the horseshoe would be convex
inferiorly

organs or vessels occasionally demands relief a displaced horseshoe
kidney for instance having been known seriously to obstruct labor
(Bugbee[5])

STATISTICAL STUDIES ON CONGENITAL RENAL ANOMALIES

Unilateral absence occurs about once in 900 autopsies (Eisendrath[8] Campbell[7] Thompson[21])

3 Various degrees of hypoplasia are ofttimes difficult to distinguish from atrophy or the end results of inflammations The clinical importance of all these groups lies in direct proportion to the reduction of functioning units

Supernumerary Kidneys —Supernumerary kidneys are rare and there are probably no more than 25 cases in the literature Kuksinskaja[14] collected 12 The smaller accessory kidney is usually anterior to the other Bumpus[6] reported 1 case and quoted a possible second (Potter and Sexton[19]) in which one kidney lay ventral to the other

Anomalies of Shape — Anomalies of shape consist of

1 Fused kidneys
2 Retention of fetal lobulation

Sokolow found the former on an average once in 864 cases while the latter occurs once in about 13 cases according to Thompson s figures [20]

Anomalies of Position — Anomalies of position may lead to diagnostic errors such as being mistaken for ovarian tumors uteri undescended testes etc The bilateral form is rare occurring perhaps once in 1000 persons (O Conor[18]) Unilateral displace-

degrees of failure to migrate to the adult position In extreme cases the kidney may remain in the pelvis Other anomalies as of the female genitalia may also be present although the adrenals usually are situated in their normal positions

Anomalies of Rotation (Brasch[3]) As the kidney migrates upward it also rotates into position so that the ureter is attached mesially hence failure to rotate and failure to migrate often are found together Failure of rotation results in anterior position of the ureter *vice versa* excessive rotation results in a posterior pelvis the latter occurrence being rare In reversed rotation the pelvis is lateral These anomalies frequently are found in connection with horseshoe kidneys where fusion during embryonic life restricts their normal movements

Anomalies of the Pelvis and Ureter —Reduplications of the pelvis " ubled ureter occur unilaterally

ureteral openings and 5
and single ureteral opening The duplicate ureters may both open into the bladder, one behind the other, or side by side, or one may

such a case the ureter may remain attached to any of the adult

organs arising from this early indifferent structure such as those mentioned above When one ureter ends blindly stenosis and atresia are the results with possible hydronephrosis or pyonephrosis Graves and Davidoff [9] relate that the ureter of a cat passed in back *of the inferior vena cava then medial to it and then crossed it* anteriorly They found 3 human cases in the literature in which a similar condition occurred 1 in an infant aged a few weeks 1 in a man aged fifty five years and 1 in a man aged eighty four years There was hydronephrosis in each case

Vascular Anomalies —Renal anomalies in structure and position are practically always accompanied by anomalies in the vessels The question arises therefore Are the former determined by the latter or the latter by the former A positive general answer is

kidneys migrate from their low position they acquire their blood supply from a new source Thus the vessels in the adult kidney have been known to come from the lower aorta from an iliac artery even from the inferior mesenteric artery The venous relations are also variable

Lisa and Levine in 1200 autopsies found the following 1 case in which the left renal vein passed posterior to the aorta 1 case in which there was a double right renal vein 8 cases in which there was a double renal artery on one side 2 cases in which there were double renal arteries on both sides 2 cases in which the renal artery entered at one pole of the kidney

Accessory vessels are fairly common usually entering the lower pole They are usually smaller than the main vessel but may be of equal size or even larger Practical aspects consist in possible torsions or compressions with resulting damage to kidney substance and also in operative procedures when vessels should not be blindly clamped and tied but identified first and the kidney mobilized to make certain no accessory vessels have been missed

CLINICAL CONSIDERATIONS OF RENAL ANOMALIES

Viewed as a whole there is unanimous agreement that the anomalous kidney is more subject to disease than the normal organ *Data as to the various forms of Bright s disease are not as* definite as those which show that the so-called surgical conditions are more common Under this are included stone formation (kidneys and ureter) hydronephrosis pyonephrosis perhaps tubercu

estimated to be about 1 in 900 The figures as to relative rates of

tumor formation in normal and anomalous kidneys and ureters leave the question open

The congenitally abnormal kidney may give no symptoms at all, ordinarily it is one of the complications which lead to its discovery, such as pressure symptoms on surrounding organs, pain and discomfort from distentions and compressions and calculi, the appearance of a mass in polycystic kidneys or in hydronephroses or pyonephroses The urine also may show no abnormalities until complications arise, whereupon pus, blood and gravel appear, or casts and the other signs of infections, injuries and perversion of function

REFERENCES

1 BOYDEN, E A 1931 Description of a horseshoe kidney associated with left inferior vena cava and disc shaped suprarenal glands, together with a note on the occurrence of horseshoe kidneys in human embryos, Anat Rec, 51, 187-212

2 ———— 1932 Congenital absence of the kidney An interpretation based on a 10-mm human embryo exhibiting unilateral renal agenesis, Anat Rec, 52, 325-339

9 FURNISS H D 1922 Supernumerary ureters with extravesical opening, J Urol, 3, 495-505

10 GRAVES, R C AND DAVIDOFF, L M 1922 Anomalous relationship of the right ureter to the inferior vena cava J Urol, 8, 75-78

11 JOLY, J S 1929 Stone and calculous disease of the urinary organs London

12 JUDD E S, BRAASCH W F, AND SCHOLL, A J 1922 Horseshoe kidney, J Am Med Assn, 79, 1189-1195

13 KRETSCHMER H L 1925 Unilateral fused kidney, Surg, Gynec and Obst, 40, 360-366

14 KUKSINSKAJA, G F 1927 Cyste in uberzahligen Niere, Ztschr f Urol, 21, 342-346

15 LEWIS, F T, AND PAPEZ, J W 1915 Variations in the early development of the kidney in pig embryos, with special reference to the production of anomalies Anat Rec, 9, 105-106

16 LISA, J R, AND LEVINE, J 1932 Renal anomalies, N Y State J Med, 3, 395

ce in

ipper

s and

Anz,

21 THOMPSON, A R 1929 (a) Solitary kidney, Guy s Hosp Rep, 79 207-219

22 ———— 1929 (b) Congenital deformities of upper urinary tract, being a continuation of previous papers on horseshoe kidney and solitary kidney Guy s Hosp Rep, 79, 351-364

CHAPTER XX

INFECTIONS OF THE KIDNEY

By HOBART A REIMANN M D

Introduction —Although the word nephritis connotes inflammation of the kidney it is used by common consent in a rather limited sense and applic [illegible]
degenerative or vascular [illegible]
of definite infections of [illegible]
terms as pyelitis pyelonephritis pyelonephrosis abscess and so on according to the anatomical character or distribution of the lesions It is with lesions of this type that this chapter deals

Classification Much depends upon point of view in the classification of infections as to whether the author is a pathologist bacteriologist or clinician It is obvious also that no two authors will agree completely on any one classification which is so well illustrated in the decades of controversy regarding nephritis itself Furthermore the function of classification is often only to preserve some degree of order in formal presentation and to establish some uniformity in nomenclature for the purpose of a common bas s for discussion In regard to infections of the kidney the pathological classification in current use is unsatisfactory unless qualified by terms indicating the specific etiological focal or urogenital factors involved Renal infections have been classified further on the basis of the pathway of infection to the kidney whether it be arterial ascending through a column of urine impounded in the ureter

infections in a previously normal kidney resulting from the lodgement of virulent organisms and as infections resulting from the deposition of any of a variety of organisms in a kidney the resistance of which has been reduced by some urogenital abnormality or condition

It seems that all of these methods of classification are inaccurate and unsatisfactory It is highly desirable therefore to decide upon a classification which will qualify some of the terms in common use by terms indicating the etiological agent wherever possible It is doubtless of greater importance to know the actual etiological

agent, its source of origin and the natural history of the infection it induces than to devote efforts in determining the gross and microscopic pathological changes or even the route of infection it traverses in reaching the kidney. It would be most desirable to establish diagnosis on a purely etiological basis as suggested forty years ago by F. Muller and later by Lahr[24] and others[17,31] but certain factors *often render this procedure difficult. Unless the organism causing* the infection can be isolated directly from the lesion as it exists in the kidney during life or in pure culture from the urine, the situation is somewhat analogous to the same problem in pneumonia. Examination of the sputum in the latter case may at once reveal the etiological agent but often a mixture of organisms is present and only by special methods can the pathogen in question be identified. Similarly, examination of the urine may also promptly settle a

one causing the infection will be found in the urine. It seems best therefore to view the disease picture as a whole regarding the possible foci of infection, clinical course of the illness and physical signs, and to correlate these with careful microscopic and bacteriological examinations of the urine and the information obtained by modern methods of urological examination. In many instances a knowledge of the natural history of an infection including its portal of entry or focus of infection will be of great assistance in diagnosis and rational therapy. The classification adopted for this presentation is based on one proposed by Hinman[31] and is satis

TABLE 98. CLINICAL-ETIOLOGICAL CLASSIFICATION OF RENAL INFECTIONS

1. Specific infections of kidneys previously normal		2. Infections with organisms mentioned in Groups I and II (most commonly colon bacilli or staphylococci) as a result of diminished resistance of the kidney due to
Group I. Focal from portal of entry elsewhere in the body. Chief manifestations of the disease in the kidney. Infection with A. Bacilli of colon typhoid group B. Staphylococcus C. Tubercle bacillus D. Treponema pallidum E. Gonococcus F. Actinomyces G. Echinococcus, etc.	Group II. Focal or metastatic from infection elsewhere or from generalized systemic disease. Chief manifestation of disease elsewhere A. Bacillary infections B. Coccal infections C. Filterable virus infections D. Spirochetal infections E. Protozoal and metazoal infections F. Fungus infections G. Rickettsial infections	Urinary obstruction or stasis from stricture, stone, neoplasm, pregnancy or other obstruction at any point of the urinary tract, faulty emptying of the bladder or congenital malformations, etc. Metastatic infection from lower urogenital tract by various routes. Contamination type, soiled diapers in infants, leukorrhea in women. Marital or defloration urethritis. Traumatic infections from foreign body, contusion, penetration, instrumental trauma followed by bacteremia

Pathogenesis —The kidneys have no free communication with the external environment Infection obviously is almost invariably conveyed to the kidneys from some focus elsewhere in the body by routes to be discussed The chief portals of entry of infection are (*a*) The urogenital tract (*b*) the gastro intestinal tract following appendicitis cholecystitis colitis or constipation (*c*) the respiratory tract following sinusitis for example and (*d*) miscellaneous foci elsewhere or systemic infectious disease The importance of colds and upper respiratory infections as causative factors has been greatly minimized by the studies of Helmholz although numerous examples are cited [16a] The part played by teeth and tonsils as foci of infection for Streptococcus viridans has been greatly exaggerated

The pathways by which infection is conveyed to the kidneys have been the subject of controversy for decades [4] It appears that the commonest routes are by way of the blood stream the ureters or the lymphatics Infection by contiguity and by penetration is less frequent

Hematogenous Infection — Bacteria are present in the blood stream much more frequently than has been realized Under ordinary circumstances they are usually harmless and the kidneys or any other organs if normal are unaffected If however the bacteria are especially virulent or if the resistance of the kidney is diminished by any of the factors about to be considered the likelihood of the localization of infection and production of lesions is greatly enhanced Bacteria reaching the kidney through the arteries either lodge as emboli in the capillaries and multiply if conditions are suitable or they may pass through the secreting
rr
be
p
observers thereafter showed that particles as large as bacteria do not pass through the membranes of a normal kidney The question is still open Brewer believed that a small number of avirulent organisms can pass the barrier Dyke [3] on the other hand showed that staphylococci passed through only after lesions had been produced Similar results with other organisms are reported by Helmholz [20] Beacham [*] Book [15] Montgomery [42a] and others The matter is of especial importance in tuberculosis of the kidney in which unfortunately differences of opinion also exist For the most part it appears that the resistance of kidney the factor of greatest importance [6] must first be diminished by mechanical obstruction by congenital abnormality by the deleterious effects of products liberated in general infections as they are excreted or by lesions produced locally in the renal capillaries by infection before bacteria appear on the distal side of the secreting membrane The site of

within the kidney.

the earliest lesions in hematogenous infection may be in the renal cortex in the region of the convoluted tubules or in the central portion of the papillæ (pyelonephritis) The primary lesion may of course be found in the pelvis of the kidney where the bacteria may be first deposited by the blood stream (pyelitis) (Fig 67) These facts emphasize the complexity of the problem and the difficulty of

infection in certain cases does reach the kidney (*a*) Through a column of urine impounded in the bladder and ureter either by growth and spread of bacteria through the fluid itself or by anti

bilities just cited always complicates the question This is illus

tance of the kidney to infection from any source The colon bacillus is most frequently encountered and is responsible for 80 or 90 per cent of infections of the ascending type

produced kidney infections in dogs by merely cutting the ureterovesical valves Lesions developed in this case without evidence of back pressure and only on the side on which the valves were cut

Lymphatic Route In the opinion of many observers the lymphatics play a minor role in carrying infection to the kidney It must be admitted ho
portion of cases An
channel includes the
cially the cervix of th

Fig 67 Infection in any of these sites could conceivably reach the kidney through the anastomosis of lymph vessels and reversal of the normal lymph flow Infection has been traced from the bladder to the kidney pelvis through the ureteral lymphatics both clinically and experimentally[460] The lymphatics no doubt, play a large rôle in the spread of infection within the kidney An intricate intercommunicating network exists in the cortex and medulla which communicates with the lymphatics of the pelvis and with those of the capsule (Fig 67, insert *a*)

Direct Infection —Direct infection may occur by penetration of the capsule itself by infection in adjacent tissues or organs, by perfor

of

is the cause or the effect of renal infections is still disputed It would seem that in the majority of cases the presence of any foreign body tends to reduce the local resistance and to predispose to infection On the other hand long standing infection with stasis and inspissation of the exudate and débris possibly results occasionally in ultimate encrustation or petrification

Bacteriology —Table 29 represents the incidence of various bacteria as found in renal infections by various observers

TABLE 29

	Schede mantel	Cabot and Crabtree	Lenhartz	Wossidlo	Kretschmer	Hellström
Colon bacilli	85	4	66	79	132	133
Staphylococci	2	23		34	28	40
Streptococci		4		34	1	6
Colon bacilli and staphylococci					10	24
Colon bacilli and streptococci						1
Staphylococci and streptococci		3			2	1
Cocci and bacilli		25				
Paratyphoid bacilli	1		3			
Gonococci	2			5		
Proteus bacilli	3		2			
Proteus and colon bacilli			1			
Influenza bacilli	2					
Cocci	5					24
Other forms				35		
No bacteria or unknown					27	13
Total	100	59	7[illegible]	187	[illegible]00	24[illegible]

The tubercle bacillus is not included in the table since renal tuberculosis is usually regarded as a separate entity and not considered with other infections Tuberculosis of the kidney in this presentation takes its relative place among other specific infections [illegible] *blastomyces, Amœba histolytica, echinococcus and others*

SPECIFIC INFECTIONS OF KIDNEYS PREVIOUSLY NORMAL

GROUP I —**Infections With Chief Manifestations of Disease in the Kidneys** —The kidneys involved in the specific infections discussed in Groups I and II were presumably normal previously Infection occurs because of the recent diminution of the resistance of the renal tissues and growth of the organisms in question

Infection Due to Bacilli of the Colon Group (Acute Pyelitis, Pyelonephritis, Chronic Pyelonephrosis) —This comprises by far the largest proportion of kidney infections It is probable, however, that the figures given in certain statistics are somewhat too high, if primary infections are indicated, since in certain instances colon bacilli invade the tissues only after the field has been prepared, so speak, by primary infection due to other organisms The primary

especially in infants and in women, which may in part be due to the proximity of the urethral orifice to the source of colon bacilli from the anus, (*b*) the vast surface presented by the intestinal tract as a potential portal of entry of colon bacilli into the blood stream, (*c*) all of the factors represented in column 3 of Table 28 Several factors not embodied in the table include various inflammatory diseases of the digestive tract as appendicitis, cholecystitis, colitis as well as constipation and hemorrhoids Colon bacillus bacteriemia is commonly present after operative manipulation or disease of the lower urinary tract Scott[31] found B coli in the blood in 40 per cent of his cases in which the urethra was the most probable portal of entry B coli sepsis occurs more frequently than is generally believed in women during the child-bearing period and in men past middle life, corresponding with the increased number of infections of the genital and urinary tract [illegible]

primary lesions occur in the kidney infected with colon bacilli

these cases were lesions present in the renal parenchyma Since the pelvic mucous membranes were solely involved he regarded these as cases of ascending infection Wilson and Schloss[68] however *believed that* severe pyuria in infants usually represents inflammation of the interstitial tissue Chown[19] and Rosenbusch[50] expressed similar views Gohrbandt[26] and others have shown that pyelitis and pyelonephritis seldom occur separately Kennedy[36] studied the kidneys of animals injected intravenously with colon bacilli and in some infected by intraureteral inoculation The early lesions of the former group were in the renal parenchyma in the region of the convoluted tubules or in the central portion of the papillae In ascending infection the primary lesion was in the pelvic lining and peripelvic tissues The infection could be traced from the bladder through the ureter and periureteral lymphatics[60] In both cases the infection spread so rapidly after reaching the kidney that it soon became impossible to determine which area was first involved The infection appeared to spread *via* the peri vascular tissues not by direct extension through the tubules Cabot and Crabtree[17] also state that lesions of ascending and hematogenous infections are indistinguishable It should also be stated at this point that hematogenous infection may originate in the kidney pelvis where the first evidences of renal inflammation appear and that ascending infection may exert its chief manifestations in the parenchyma The point to be emphasized is that the route of infection and its mode of spread is of secondary importance as compared with the existence location and etiological factors of the primary focus

Pathology[4]—Kretschmer[37] reported that among 169 cases of pyelitis mostly due to the colon bacillus 120 were bilateral 32 inv [illegible] 7 the left In the acute stage of [illegible] usually enlarged some tin [illegible] appears congested and mc [illegible] with yellowish gray lines The mucosa of the pelvis is usually inflamed and pus may be found in the lumen In long standing chronic cases *the cortex may be thinned or completely* absent leaving only a shell Microscopically there is often evidence of acute inflammation of the tubules while the pyramids may be free There may be edema and extensive *polymorphonuclear* and lymphocytic infiltration and areas of necrosis (abscesses) of the interstitial tissue peripelvic areolar tissue and pelvic epithelium The tubules are often dilated and filled *with masses of desquamated* epithelium bacteria and pus Bacilli

are occasionally found in the interstitial tissues Microscopic abscess formation is usually caused by the confluence of destructive processes involving groups of tubules Glomeruli are involved only by direct extension of inflammation Healing when it does occur is rapid and often leaves scar tissue though seldom enough to interfere with normal excretion In chronic cases most of the kidney substance may be destroyed

attention to the disease and often dominate the picture throughout Frequency urgency burning or pain on urination turbid urine and hematuria are common complaints The manifestations vary greatly Acute pyelitis or pyelonephritis may be entirely silent as to local symptoms even when severe or may give rise to marked local and general symptoms when relatively mild Usually but not always

kidney regio

stretching of

regions especially on hammer percussion The kidney may be palpable and tender The symptoms may suggest acute cholecystitis or appendicitis

The general symptoms may commence insidiously but usually with a sudden chill and fever Abdominal distention anorexia malaise chills and sweats are common Vomiting may occur The fever curve is often of the remittent type and usually lasts from three to ten days Herpes simplex commonly occurs

The infection tends to heal spontaneously unless the causative factors mechanical or infectious remain Under the latter con

fever occasional chills cachexia and may succumb to exhaustion secondary infection or may pass into uremia because of loss of

be

ab

toi

sti

ca

a tight fitting uterus in an inelastic pelvis and to other causes which interfere with the normal outflow of urine Infection is commonest in primipara during the fifth to the seventh months of pregnancy The usual signs and symptoms occur Relapses are apt to recur in succeeding pregnancies

The urine contains pus because the colon bacillus affects chiefly the renal pelvis and tubules *The quantity of pus bears no constant* relationship to the severity of the process In rare cases in which the lesions are in the cortex the urine may be clear Albuminuria

tion They may be present merely because of reduced resistance induced by infection due to other organisms The quantity of urine at first is often diminished but may be increased later in the course The urine in chronic cases may be thick yellowish green and foul smelling

Diagnosis —Diagnosis rests on many of the points just discussed Modern urological methods of cystoscopy, ureteral catheterization and roentgenographic studies have simplified diagnosis and frequently permit a diagnosis to be made early in the course of disease [8] Instrumentation may be harmful in the acute stage Intravenous pyelography is valuable in certain cases not suited to catheterization

In many cases the symptoms caused by conditions which were the ultimate cause of the renal infection dominate or obscure the picture In the typical acute case the bladder symptoms in addition to pain in the lumbar region and the symptoms of general infection point to renal infection The cystoscope should be used gently and only when definite indications exist for it is impossible even with the best of technique to avoid a certain amount of trauma which so often serves as a portal of entry for colon bacilli into the blood stream Cystoscopy and ureteral catheterization especially when aided by roentgenographic study are highly valuable in determining the presence or absence of abnormality and whether one or both kidneys are involved The presence of stones dilatations or narrowing of the calyces the amount of destruction in

be demonstrated in

with colon bacilli

ise of the involve

ment of the secreting tubules This often serves to distinguish colon bacillus infection from staphylococcal or other infections affecting chiefly the cortex in which the secretory power is less affected In acute unilateral colon bacillus infections there is no retention of metabolites in the blood when both kidneys are involved retention may occur

Beckman[10] demonstrated specific agglutinins in the blood in cases

of colon bacillus pyelonephritis Bitter and Gundel[14] believed that hemolytic colon bacilli produced severe symptoms of acute disease, while non-hemolytic strains tended to cause lower-grade and chronic infections Lowenberg[39] found that the hemolytic variety was the most common etiological agent

When examining the urine it is absolutely essential to obtain "clean" specimens Urine in colon bacillus infections is said to be acid, from staphylococcal infections, alkaline Pyuria and hematuria are present In the past, much emphasis was placed on the fact that urine from cases of pyelonephritis when filtered through paper remained cloudy, while urine from cystitis filtered clear Careful microscopic and cultural studies must be made of the urine of each kidney separately Care must be exercised not to overlook other organisms, especially tubercle bacilli, even though colon bacilli are present A sterile urine in pyelonephritis should suggest tuberculosis Casts containing pus and blood cells occur

Th

rev

Th

When both kidneys are involved, signs and symptoms of uremia may develop Pyelograms show evidence of destruction of the pelvis and cortex

Treatment —Most of the acute cases recover spontaneously if the predisposing factors or foci of infection are eliminated It is said that in general 50 per cent recover completely, 30 per cent have relapses and 20 per cent become chronic General treatment

Chief attention should be devoted to the detection and elimination of contributing factors and foci of infection, many of which are mentioned on page 307

Very little can be accomplished in the actual treatment of pyelitis or pyelonephritis in itself Residual bladder urine, in cases of obstruction, should not be permitted to reaccumulate If, during cystoscopy, no urine can be seen coming from one ureteral orifice, drainage should be reestablished by ureteral catheterization Release of urine impounded by obstruction of the ureter with pus and debris or other cause often gives striking relief from pain

The

the

able

trac

to further complications instead of relief Many believe it desirable to alter the reaction of the urine, since colon bacilli grow best

within certain degrees of acidity and alkalinity The sudden and repeated alteration of the reaction of the urine from acid to alkaline it is said, renders growth conditions for the bacilli unfavorable Sodium bicarbonate 4 [illegible]
or potassium or sodiu [illegible]
day, for a day or two [illegible]
or two of acidity, induced by, acid sodium phosphate, 2 gm (30 grains), or ammonium chloride 2 gm (30 grains), four times a day or more, until the urine is acid to methyl red, is recommended Successful results are reported in the treatment of chronic pyelitis, especially in children by the use of a ketogenic diet as suggested by Helmholz Under this regime, attempts are made to keep the pH of the urine below 5 5 and to attain a concentration of about 1 per cent β hydroxybutyric acid in the urine Ammonium chloride may be used to assist in the acidification of the urine The water intake should be restricted during the treatment

Surgical procedures (decapsulation) as a rule, are not recommended in acute cases In certain selected instances, however nephrostomy appears to give striking relief In chronic cases or under special circumstances in acute cases, when one kidney is involved, nephrectomy should be considered When nephrectomy is necessary it should not be delayed lest both kidneys become involved

Drug Therapy —Although much has been written on the subject, the reports of benefit derived therefrom are most unconvincing The long list of drugs recommended attests to this statement The hope of sterilizing the kidney pelvis with antiseptic lavage is futile A cursory consideration of the underlying pathology and the penetration of infection deep into the tissues renders such procedures illogical Even if the infection were superficial, it is doubtful whether the field could be sterilized without destroying the tissue itself Careful critical studies of some of the newer complex chemical compounds recently recommended have confirmed their efficacy against various bacteria when suspended in plain broth in the test tube, but the addition of small amounts of urine and especially of serum, at once diminishes or destroys bactericidal activity Similar remarks apply to the use of many substances recommended for intravenous medication Controlled experiments do not justify their use clinically Nevertheless further work [illegible] The use of

[illegible]

purely experimental

Infections of the Kidney Due to Colon Bacilli and Pyogenic Cocci — Kidneys in which resistance has been reduced by infection with other

the invasion of pyogenic cocci These facts probably account for

cultures are secured from various portions of the kidney when sectioned the results are apt to be misleading—for bacilli alone may be found in one area cocci in another and both in a third [17]

The pathology and symptoms of mixed infections are obviously confused and may be most typical of the infections discussed preceding or of those succeeding this subgroup depending upon the predominance of effects of either one or the other organism

Staphylococcal Infection of the Kidney [5] This infection gives rise to lesions described as suppurative nephritis kidney abscesses carbuncle of the kidney septic infarct or acute pyonephrosis It seems simpler however to regard the lesions as cortical infections caused by the staphylococcus differing only in number size distribution degree of coalescence and age Lesions caused by the staphylococcus often extend toward the surface of the kidney either through the lymphatics or by contiguity pass through the capsule and cause perinephritic abscess The infection is usually acute but may become subacute or chronic

The relative incidence of staphylococcal infections of the kidney is shown in Table 29 The frequency of infection is probably dependent upon the frequency with which the staphylococcus invades the blood stream Various factors render the kidney subject to infection Males are more frequently affected than females probably because of greater exposure to trauma and skin infections The lesion is frequently unilateral In Nesbit's[43] series the right side was affected in 31 cases the left in 12 and both in 5 It seems probable that necropsy studies would reveal a much higher percentage of cases with bilateral

healed Occasionally no focus can be found and the infection appears to be primary in the kidney Many cases of staphylococcus infection elsewhere in the body occur in which specific kidney lesions develop but only as a minor factor and are often not recognized clinically [25] These forms fall into Group II

Pathology—The infected kidney is usually enlarged from congestion and edema. Scattered abscesses may be seen protruding or a single large carbuncle may be present. In the early stages the cut surface may reveal a variable number of abscesses of different sizes scattered throughout the cortex or there may be one large area of suppuration (carbuncle, septic infarct). The entire parenchyma is seldom involved. The medulla is seldom seriously affected and the pelvis usually escapes so that unless an abscess ruptures into the pelvis pyuria does not occur. In later stages the abscesses may enlarge and become confluent. They may perforate the cap

and evolution of the lesions are similar to those caused by staphylococcus elsewhere in the body. The lesions are often found in various stages of development from the earliest inflammation to complete healing. Widespread lesions may heal with almost complete restoration of the normal parenchyma. Occasionally B coli appears as a secondary invader and causes infection which may outlast the original one. Staphylococci may be present in the kidney pelvis without evidence of pyelitis.

Symptoms—The symptoms may be chiefly referable to the kidney or may be entirely constitutional with little or no evidence of renal disturbance. In the typical case there is frequently a history of minor infection elsewhere in the body followed by a sudden chill, fever, pain and tenderness in the costo vertebral angle. The pain is usually of moderate severity and constant but occasionally is of the renal colic type and radiates down the ureters. Cystitis occasionally complicates the infection. Chills and sweating may recur. Otherwise the general symptoms of acute infection are present including anorexia, malaise, remittent fever and leukocytosis averaging 15 000. Vomiting is uncommon. Initial oliguria may occur.

others claim that only rarely do acute uncomplicated staphylococcus infections become chronic. Perinephritic abscess occurs in perhaps 10 per cent of cases.

The urine may be normal except for traces of albumin common to most infections. Nesbit[13] found staphylococci in the urine at some stage of the disease in each of his 48 cases. Occasionally no growth occurred when samples of certain urine specimens in which staphylococci were seen were cultivated on artificial media. Gross and microscopic hematuria occur in a relatively small percentage of cases. Pus cells are seldom found unless an abscess ruptures

into the pelvis or unless the tubules are invaded or colon bacilli become secondary invaders

[illegible]

Tenderness on hammer percussion may be of value, but it is often present in normal individuals The kidney may be palpable and tender The presence of staphylococci in the urine or in the blood stream is strongly suggestive The identification of staphylococci from pus aspirated with an exploring needle from a swelling in the lumbar region is of great value especially when perirenal suppuration is present Ureteral catheterization assists in determining whether one or both kidneys are involved if surgical intervention is considered The phenolsulphonephthalein test is usually normal The urine is said to be alkaline in reaction Other conditions such as acute appendicitis, cholecystitis or other abdominal inflammation, may be confusing Acute hydronephrosis can be detected by ureteral catheterization or by roentgen-ray studies

Treatment —Although general opinion has strongly favored nephrectomy if the involvement can be proved to be unilateral

[illegible]

ordinarily unnecessary Decapsulation is not recommended Surgical drainage is usually required for perirenal abscess In certain chronic complicated cases with unilateral involvement, nephrectomy is necessary Antiseptics injected into the urinary tract or into the blood stream or given otherwise are useless The use of specific bacteriophage is as yet unwarranted

Tuberculosis of the Kidney[6]—Tuberculosis of the kidney comprises from 15 to 24 per cent of renal infections found at necropsy Clinically the percentage is much lower About 10 per cent of tuberculosis patients examined at necropsy show tuberculous lesions in the kidneys Medlar[42] found renal tuberculosis in 22 out of 30 cases of advanced tuberculosis The involvement was bilateral in each case Wildbolz[57] believes that in the early period only one kidney is affected Only 12 per cent of his 1000 cases were bilateral Other observers report bilateral involvement in about 50 per cent of cases[56] Accurate knowledge on this point would be of great importance considering the benefit frequently obtained in suitable cases by nephrectomy

Renal infection is usually secondary to active infection elsewhere, in 30 to 50 per cent of cases in the lungs and 15 to 25 per cent in the genitalia In certain cases, the lesion appears to be primary

in the kidney—at least the dom[illegible]

urinary system [illegible]

life Males are [illegible]

blood-borne The possibility of ascending infection is denied by [illegible]

circumstances suitable for growth in the tissues of the lower urinary tract The rôle of hypersensitivity in the development of renal tuberculosis is at present uncertain

There is no selective action of tubercle bacilli for renal tissue Infection may be the result of constant seeding of bacilli carried by the blood stream from a distant focus and deposited in tissues whose resistance has been reduced by 'toxemia' accompanying the infection Lodgement and growth of bacilli, hypersensitivity and any of the factors of mechanical interference already mentioned may predispose the kidney to infection According to Medlar,[42] the first lesions most frequently arise in the glomeruli or tissues between the tubules in the cortex and occasionally in the papillæ or in both localities The lesions were cortical in 75 per cent of his cases, medullary in 11 per cent and were present in both areas in 13 per cent Cabot and Crabtree[17] and others found the earliest lesions at the base of the pyramids Wildbolz[57] found them localized near the papillæ and calyces Extension to other areas takes place through the interlobular lymphatics and may involve the subcapsular lymphatics (Fig 67, insert *a*)

As mentioned previously, the significance of the presence of tubercle bacilli in urine has been much debated A number of competent observers claim that tubercle bacilli may be secreted by a kidney which shows no evidence of tuberculosis pathologically Others believe that tubercle bacilluria always indicates some degree of kidney involvement no matter how minimal [38, 57] In certain cases of tubercle bacilluria due to one tuberculous kidney, bacilli are occasionally found in urine obtained from the sound side Their presence there, according to Wildbolz, may be due to reflux up the ureter or to contamination of the catheter during its passage upward It, therefore cannot be accepted that the presence of tubercle bacilli in the urine alone is evidence of tuberculosis of the kidney

Pathology —Grossly the kidney may appear normal except when large tubercles appear near the surface When large caseous areas are present, the kidney may appear lobulated and feel boggy Less frequently the kidney is uniformly enlarged, due to fibrous or fatty infiltration without cavity formation, or the kidney may be

shrunken with all renal tissue replaced by scar tissue caseous or calcified areas The perirenal tissues may be involved

Wildbolz considers three general forms (*a*) Nodular or caseo-cavernous characterized by discrete or confluent tubercles of varying sizes distributed throughout the cortex and medulla similar to the specific lesions found elsewhere in the body In later stages caseation and cavitation are found Tubercles may involve or rupture into the pelvis causing tuberculous pyelitis The lesions may be entirely confined to one kidney but when the disease has become chronic both are usually involved one more than the other The cavities gradually enlarge and coalesce Ultimately the tuberculous process involves the ureters and bladder Stricture of the ureter may cause pyonephrosis (*b*) In the fibrotic or indurative form caseation does not occur instead the tubercles become *encapsulated or fibrotic* (*c*) *In tuberculous nephritis character-*
[illegible] al
[illegible] a
[illegible] m
ably partly due to the toxic effects of the soluble substances liberated *in situ* Similar lesions have been produced experimentally by the injection of tuberculin or of other products of tubercle bacilli A number of observers however doubt the existence of a tuberculous nephritis All three forms may give rise to pyuria and bacilluria Amyloid deposits are often found in the chronic cases In Wessel's[58] series the pathological changes found at necropsy were grouped as follows Miliary tuberculosis 115 pyelonephritis 30 pyonephrosis 11 nodular parenchymatous tuberculosis 9 isolated cavitation 8 tuberculous infarcts 5 caseous medullary foci 2

Histologically the typical tuberculous lesions are like those found elsewhere in the body Unless the process has progressed to the state of caseation and destruction healing with scar formation may occur just as healing of tuberculous lesions elsewhere in the body may take place

Symptoms—Early tuberculosis of the kidney is most often symptomless for long periods or masked by symptoms of infection elsewhere Local manifestations arise when abscesses or cavities become large enough to interfere with normal drainage or when secondary infection takes place *Wildbolz proposes the onset be grouped into four classes* (*a*) *Cystitis the commonest early symptom* (*b*) renal colic with lumbar pain radiating downward with

and stretching of the capsule or to the colic incident to the intermittent blockage of the ureter by the passage of clumps of pus debris or clots Hematuria gross or microscopic is frequently noted

in the lu

Perirenal

may persist for years with remissions and relapses the condition gradually growing worse General symptoms may be absent for long periods of time but usually there are night sweats loss of

Extensive involvement may

ral reaction and small lesions

ft untreated the outcome is

usually fatal

Diagnosis All efforts should be made to establish early diagnosis before destruction has advanced too far Early diagnoses are being made more and more frequently due to increased knowledge and to improvements in urological diagnostic methods[8] The *presence of tuberculosis elsewhere in the body and the appearance*

in urine obtained by ureteral catheters by stained smear or cultural methods or by guinea pig inoculation The problem referred to before in deciding whether a kidney which is excreting tubercle bacilli is *tuberculous or not may indeed be difficult* Retrograde pyelography is of distinct value in doubtful cases In the earliest stage it m he tips of the papillæ Retrograde pyelograph the opposite kidney is sound or not

The amount of urine excreted may be normal Polyuria may occur in unilateral disease and oliguria may exist in bilateral involvement Albuminuria commonly occurs Pyuria occurs when the pelvis and lower urinary tract becomes infected Gross or microscopic hematuria is common Urine from a severely involved kidney may be impounded so that the bladder urine which comes

lesion in the kidney although it is very suggestive Other tubercu lous foci for example in the prostate may shed tubercle bacilli into the urine It is at present often impossible to distinguish clinically between the various forms of tuberculous involvement of the kidney Certain differential points have been noted The secretory function of the kidney as measured by dye tests is more

rapidly reduced in the caseous forms than in so-called tuberculous nephritis There is often a marked delay and decrease in the excretion of indigo-carmine and of urea The "toxicity" which occurs during the caseous forms is greater In the late stages of tuberculous nephritis marked disturbances of function occurs

Prognosis —It is generally recognized that most cases of untreated renal tuberculosis end fatally, often within a year or two On the

after operation The remainder succumbed chiefly to tuberculosis of the opposite kidney, to pulmonary or miliary tuberculosis and 15 per cent died from other intercurrent diseases The immediate mortality among selected cases operated upon was about 2 5 per cent

never heal completely

Treatment [1 8 11]—The ideal subject for nephrectomy is one without active tuberculous infection elsewhere whose general condition is good and in whom tuberculous caseation and cavitation are limited to one kidney Nephrectomy is contraindicated in definite bilateral infection or during active tuberculosis elsewhere Careful examination and good judgment are needed All efforts should be made to determine whether tubercle bacilluria if present, is due to reflux of infected urine from the bladder, to contaminated catheters and whether the actual process in the kidney is of the type regarded by some as tuberculous nephritis or is actually caseating and destructive When the destruction is unilateral nephrectomy is indicated If there is doubt whether the condition is of one or another type the patient should be observed for several months

Syphilis of the Kidney [6]—Syphilitic nephritis has been described by Stoeckenius[53] and Rich[49] The latter found 13 cases among

surface of the kidney showed glistening flecks often several millimeters in diameter The cut surface showed grayish-white flecks and streaks replacing the striæ and extending to the medulla In later stages of healing, large scars caused a roughened appearance of the whole kidney akin to hepar lobatum The process varies greatly in extent It may be diffuse and destroy large portions of

and stretching of the capsule or to the colic incident to the intermittent blockage of the ureter by the passage of clumps of pus debris or clots Hematuria gross or microscopic is frequently noted In later stages there is often a sense of fulness or discomfort in the lumbar region and the kidney may be palpable and tender Perirenal involvement intensifies the symptoms The symptoms may persist for years with remissions and relapses the condition gradually growing worse General symptoms may be absent for long periods of time but usually there are night sweats loss of weight malaise and afternoon fever Extensive involvement may be accompanied by but slight general reaction and small lesions may cause profound illness If left untreated the outcome is usually fatal

Diagnosis —All efforts should be made to establish early diagnosis before destruction has advanced too far Early diagnoses are being made more and more frequently due to increased knowledge and to improvements in urological diagnostic methods [8] The presence of tuberculosis elsewhere in the body and the appearance of urinary symptoms should cause suspicion All cases of persistent pyuria especially if the pus is sterile should be suspected as tuberculous Frequent careful search should be made for tubercle bacilli in urine obtained by ureteral catheters by stained smear or cultural methods or by guinea pig inoculation The problem referred to before in deciding whether a kidney which is excreting tubercle bacilli is tuberculous or not may indeed be difficult Retrograde pyelography is of distinct value in doubtful cases In the earliest stage it may reveal minute areas of destruction at the tips of the papillæ In late cases large cavities may be evident Retrograde pyelography is often valuable in determining whether the opposite kidney is sound or not

The amount of urine excreted may be normal Polyuria may occur in unilateral disease and oliguria may exist in bilateral involvement Albuminuria commonly occurs Pyuria occurs when the pelvis and lower urinary tract becomes infected Gross or microscopic hematuria is common Urine from a severely involved kidney may be impounded so that the bladder urine which comes from the sound organ may be normal Failure to find bacilli does not rule out tuberculosis In rare cases tubercle bacilluria may be the only abnormality In early cases the presence of bacilluria with or without pus cells does not necessarily indicate a destructive lesion in the kidney although it is very suggestive Other tuberculous foci for example in the prostate may shed tubercle bacilli into the urine It is at present often impossible to distinguish clinically between the various forms of tuberculous involvement of the kidney Certain differential points have been noted The secretory function of the kidney as measured by dye tests is more

rapidly reduced in the caseous forms than in so-called tuberculous nephritis There is often a marked delay and decrease in the excretion of indigo-carmine and of urea The "toxicity" which occurs during the caseous forms is greater In the late stages of tuberculous nephritis, marked disturbances of function occurs

Prognosis—It is generally recognized that most cases of untreated renal tuberculosis end fatally often within a year or two On the other hand, patients may survive for many years without suffering much disability Among 270 cases in which nephrectomy had been performed by Wildbolz, about 60 per cent were alive ten years after operation The remainder succumbed chiefly to tuberculosis of the opposite kidney, to pulmonary or miliary tuberculosis and 15 per cent died from other intercurrent diseases The immediate mortality among selected cases operated upon was about 2 5 per cent [illegible]

never heal completely

Treatment[1 8 11]—The ideal subject for nephrectomy is one without active tuberculous infection elsewhere whose general condition is good and in whom tuberculous caseation and cavitation are limited to one kidney Nephrectomy is contraindicated in definite bilateral infection or during active tuberculosis elsewhere Careful examination and good judgment are needed All efforts should be made to determine whether tubercle bacilluria if present, is due to reflux of infected urine from the bladder, to contaminated catheters and whether the actual process in the kidney is of the type regarded by some as tuberculous nephritis or is actually caseating and destructive When the destruction is unilateral, nephrectomy is indicated If there is doubt whether the condition is of one or another type, the patient should be observed for several months [illegible]

Syphilis of the Kidney[6]—Syphilitic nephritis has been described by Stoeckenius[53] and Rich[49] The latter found 13 cases among [illegible]

surface of the kidney showed glistening flecks often several millimeters in diameter The cut surface showed grayish-white flecks and streaks replacing the striæ and extending to the medulla In later stages of healing, large scars caused a roughened appearance of the whole kidney akin to hepar lobatum The process varies greatly in extent It may be diffuse and destroy large portions of

and stretching of the capsule or to the colic incident to the intermittent blockage of the ureter by the passage of clumps of pus débris or clots Hematuria gross or microscopic is frequently noted

in the lu

Perirenal

may persist for years with remissions and relapses the condition gradually growing worse General symptoms may be absent for long periods of time but usually there are night sweats loss of weight malaise and afternoon fever Extensive involvement may be accompanied by but slight general reaction and small lesions may cause profound illness If left untreated the outcome is usually fatal

Diagnosis All efforts should be made to establish early diagnosis before destruction has advanced too far Early diagnoses are being made more and more frequently due to increased knowledge and to improvements in urological diagnostic methods [8] The presence of tuberculosis elsewhere in the body and the appearance of urinary symptoms should cause suspicion All cases of persistent pyuria especially if the pus is sterile should be suspected as tuberculous *Frequent careful search should be made for tubercle bacilli* in urine obtained by ureteral catheters by stained smear or cultural methods or by guinea pig inoculation The problem referred to before in deciding whether a kidney which is excreting tubercle *bacilli is tuberculous or not may indeed be difficult* Retrograde pyelography is of distinct value in doubtful cases In the earliest stage it may reveal minute areas of destruction at the tips of the papillæ In late cases large cavities may be evident Retrograde pyelography is often valuable in determining whether the opposite kidney is sound or not

The amount of urine excreted may be normal Polyuria may occur in unilateral disease and oliguria may exist in bilateral involvement Albuminuria commonly occurs Pyuria occurs when the pelvis and lower urinary tract becomes infected Gross or microscopic hematuria is common Urine from a severely involved kidney may be impounded so that the bladder urine which comes from the sound organ may be normal Failure to find bacilli does not rule out tuberculosis *In rare cases tubercle bacilluria may* be the only abnormality In early cases the presence of bacilluria with or without pus cells does not necessarily indicate a destructive lesion in the kidney although it is very suggestive Other tuberculous foci for example in the prostate may shed tubercle bacilli into the urine It is at present often impossible to distinguish t of

rapidly reduced in the caseous forms than in so-called tuberculous nephritis There is often a marked delay and decrease in the excretion of indigo-carmine and of urea The 'toxicity' which occurs during the caseous forms is greater In the late stages of tuberculous nephritis, marked disturbances of function occurs

Prognosis—It is generally recognized that most cases of untreated renal tuberculosis end fatally, often within a year or two On the other hand patients may survive for many years without suffering much disability Among 270 cases in which nephrectomy had been performed by Wildbolz about 60 per cent were alive ten years after operation The remainder succumbed chiefly to tuberculosis of the opposite kidney, to pulmonary or miliary tuberculosis and 15 per cent died from other intercurrent diseases The immediate mortality among selected cases operated upon was about 2 5 per cent Complete healing and scar formation with more or less diminution of function may occur in the types regarded as tuberculous nephritis or fibrosis It is probable that caseating and destructive lesions never heal completely

Treatment[1 8 11]—The ideal subject for nephrectomy is one without active tuberculous infection elsewhere whose general condition is good and in whom tuberculous caseation and cavitation are limited to one kidney Nephrectomy is contraindicated in definite bilateral infection or during active tuberculosis elsewhere Careful examination and good judgment are needed All efforts should be made to determine whether tubercle bacilluria, if present, is due to reflux of infected urine from the bladder, to contaminated catheters and whether the actual process in the kidney is of the type regarded by some as tuberculous nephritis or is actually caseating and destructive When the destruction is unilateral nephrectomy is indicated If there is doubt whether the condition is of one or another type the patient should be observed for several months

Syphilis of the Kidney[6]—Syphilitic nephritis has been described by Stoeckenius[53] and Rich[43] The latter found 13 cases among

surface of the kidney showed glistening flecks often several millimeters in diameter The cut surface showed grayish white flecks

greatly in extent It may be diffuse and destroy large portions of

*and stretching of the capsule or to the colic incident to the inter*mittent blockage of the ureter by the passage of clumps of pus debris or clots Hematuria gross or microscopic is frequently noted

in the lu

Perirenal

may persist for years with remissions and relapses the condition gradually growing worse General symptoms may be absent for long periods of time but usually there are night sweats loss of weight malaise and afternoon fever Extensive involvement may be accompanied by but slight general reaction and small lesions may cause profound illness If left untreated the outcome is usually fatal

Diagnosis All efforts *should be made to establish early diag*nosis before destruction has advanced too far Early diagnoses are being made more and more frequently due to increased knowledge and to improvements in urological diagnostic methods [8] The presence of tuberculosis elsewhere in the body and the appearance

All cases of persistent

in urine obtained by ureteral catheters by stained smear or cultural *methods or by guinea pig inoculation The problem referred to* before in deciding whether a kidney which is excreting tubercle bacilli is tuberculous or not may indeed be difficult Retrograde pyelography is of distinct value in doubtful cases In the earliest stage it may reveal minute areas of destruction at the tips of the papillæ In late cases large cavities may be evident Retrograde pyelography is often valuable in determining whether the opposite kidney is sound or not

The amount of urine excreted may be normal Polyuria may *occur in unilateral disease and oliguria may exist in bilateral involve*ment Albuminuria commonly occurs Pyuria occurs when the pelvis and lower urinary tract becomes infected Gross or microscopic hematuria is common Urine from a severely involved kidney may be impounded so that the bladder urine which comes from the sound organ may be normal Failure to find bacilli does not rule out tuberculosis In rare cases tubercle bacilluria may be the only abnormality In early cases the presence of bacilluria with or without pus cells does not necessarily indicate a destructive *lesion in the kidney although it is very suggestive* Other tuberculous foci for example in the prostate may shed tubercle bacilli into the urine It is at present often impossible to distinguish

the parenchyma The tubules may be primarily or secondarily involved by pressure of the newly formed granulomata Microscopically typically granulomatous syphilitic lesions are present although Rich was unable to detect spirochetes Warthin showed that the interstitial tissue is primarily attacked by the spirochetes which then pass through the walls of the tubules into the lumina The glomeruli are not primarily damaged

Diffuse or conglomerate gummata or diffuse syphilitic patches have been occasionally noted in the cortical region usually affecting one kidney Evidence of large gummata can sometimes be visualized by pyelography The histology is typical of syphilitic lesions found elsewhere Congenital syphilis is manifested chiefly by microscopic changes gummata are rare

Symptoms —When clinical or laboratory evidence of nephritis appears during syphilis it is necessary to suspect its specific origin The kidneys may presumably be damaged by the excretion of injurious substances elaborated by the infection at a distance or locally When the kidney tissue has been largely destroyed by the specific process the signs and symptoms of uremia occur It has been suggested that active antisyphilitic treatment in itself may damage the kidney and it is therefore sometimes withheld when evidence of renal impairment is found Knowing the possibilities of actual specific infection and the unlikelihood of kidney damage resulting from proper therapy antisyphilitic treatment should be continued in spite of evidence of kidney disease Indeed evidence of nephritis or nephrosis often disappears under active therapy

Gonococcus Infection of the Kidney Gonococcus infection of the kidney is a rare occurrence Reports of ?8 cases have been collected by Johnson and Hill[33] The organism was positively [illegible] 15 of these cases Morpho [illegible] observers believe [illegible] cends from the primary urethral lesions by the backflow of urine through the lymphatics or by inflammation migrating along the ureters Many cases are complicated by urethral or ureteral strictures and hydronephrosis or pyonephrosis In many cases colon bacilli or other organisms appear as secondary invaders In the typical case the lesion consists of intense follicular inflammation in the pelvis Distinct abscesses may occur[5] Destruction of the parenchyma and pyonephrosis often result from chronic obstruction

Clinically the symptoms may resemble those of tuberculosis but usually are uncharacteristic and depend upon the situation extent and severity of the lesions and the degree of obstruction or destruction present Clinical diagnosis is often presumptive and suspected from the history or presence of urethral gonorrhea or by the presence

of gonococci and pus in the urine obtained by ureteral catheterization The blood culture may be positive in severe acute cases The prognosis is unfavorable Endocarditis or other metastatic infections may occur

Treatment —The treatment is usually symptomatic The primary forms should be eradicated Nephrectomy is indicated in chronic forms with unilateral involvement and destruction

Actinomycosis —Actinomycosis is an uncommon disease in general and rarer still as a "primary" infection of the kidney Obviously the portal of entry or primary focus must exist elsewhere in the body, in the skin, the lungs the intestinal tract or elsewhere When the primary focus is located in the skin, for example, and recognized as actinomycosis, diagnosis of invasion of the kidney is simplified In certain rare instances, however, the chief manifestations occ

reports of

and unilat

culosis or

years with slowly developing anemia, cachexia and eventual death The infection may burrow and penetrate into the abdominal cavity or externally Metastatic infections often develop elsewhere and render diagnosis possible during life The chief clinical features are localized pain, low-grade fever, anemia, cachexia muscle rigidity anteriorly or posteriorly over the kidney region and a palpable mass which may or may not be tender The sudden appearance of acute symptoms in the course of the illness may indicate superimposed infection by other organisms or the rupture of an abscess into the pelvis or through the renal capsule Except when the pelvis is involved the urine is normal or perhaps contains a few red blood cells Renal function of the involved kidney is unimpaired in the early stages In the advanced cases the kidney may be destroyed The perirenal tissue may be invaded, producing the "woody" sense of hardness of the abdominal wall or lumbar region, said

tio

for

in long-standing cases

Diagnosis —Unless the disease is in mind, cases are most frequently regarded as tuberculosis or tumor of the kidney because of the clinical signs symptoms and chronicity Pyelograms may show evidence of destruction or of compression of the pelvis When an abscess ruptures into the pelvis, the process is apt to be regarded

21

as *suppurative pyelitis* The urine should be carefully and repeatedly examined for the fungus Acid fast rods must be differentiated from tubercle bacilli by guinea pig inoculation or by culture on artificial media The diagnosis becomes evident when the typical granules are found in the urine in pus from metastatic lesions in accessible parts of the body from pus aspirated from the local lesion or in tissue removed at biopsy and examined histologically *and bacteriologically* The organisms can be cultivated in artificial media or injected into experimental animals for further identification

Prognosis Unless the process is actually localized in one kidney and removed by nephrectomy the disease is invariably fatal in several months or years

Treatment — The treatment resolves itself to surgical removal of the infected tissue if the process does not exist elsewhere as well *Drug therapy is without specific value*

Echinococcus Cyst or Hydatid Disease — Echinococcus cyst or hydatid disease of the kidney [321] like the preceding infection is rare Kretschmer in 1923 collected 18 cases reported in North America and several have since been added The Echinococcus granulosus is a minute tapeworm infesting chiefly the dog s intestine Its eggs are shed in the feces and find their way to the intestinal *tract of man The eggs hatch enter the portal circulation and* usually lodge in the liver They may pass this barrier and come to rest in other organs in the kidney for example in about 2 per cent of cases Once located they develop into unilocular cysts filled with serous or gelatinous fluid and become surrounded by a tough fibrous wall The inner germinal layer produces buds or daughter cysts which may remain attached or float free in the fluid Rupture of the cyst liberates the daughter cysts each of which is capable of producing another large cyst

The disease is almost always unilateral and usually a single cyst is present In the early stage the cyst merely acts as a foreign body simulating a tumor It may reach the size of a football and destroy the kidney by pressure The symptoms and signs are those of renal tumor There is often a sense of fulness or uneasiness in the lumbar region and a mass may be seen or felt The general health may be unaffected *Hematuria may be present* Secondary infection or rupture of a cyst into the pelvis may be followed by symptoms of cystitis or pyelonephritis The course of the disease may be punctuated by attacks of pain caused by the passage or [illegible] the ureter

[illegible]

discharge of the cyst contents Usually it results in death by exhaustion by extension to other organs or by intercurrent infection

[illegible] when the [illegible] With [illegible] careful urological studies were able to diagnose [illegible] of [illegible] cases before operation Diagnosis is easy when the cyst is aspirated or ruptures spontaneously and daughter cysts or hooklets are found in the aspirated fluid or in the urine or when cysts appear in other parts of the body Pyelography may reveal compression of the pelvis but may show nothing abnormal Calcified hydatid cysts can be visualized by the roentgenograph Eosinophilia occurs in 50 per cent of cases The test of Casoni (the intradermal injection of 0 2 cc of pooled sterile fresh hydatid cyst fluid produces an urticarial wheal in infected individuals) is of value in diagnosis The complement fixation test of Ghedini is also used

Treatment The treatment is surgical Marsupialization is recommended Conservative operation is justified in localized cysts nephrectomy when the diagnosis is in doubt or when the cyst has perforated the renal pelvis Prophylaxis against infection in infested regions should be practised

Group II —**Infections of the Kidney With Chief Manifestations of Disease Elsewhere** The infections discussed in Group I fall into Group II when the symptoms signs and pathology of the kidney disease are overshadowed by the manifestations of the infection at the original site of entry in other metastatic lesions or by generalized disease In many of the entities discussed in Group II however involvement of the kidneys is always of minor importance and seldom gives rise to evidence of clinical disease When clinical symptoms and signs appear they depend upon the parts of the kidney most involved and on the extent of the process These lesions are usually bilateral and heal when the original infection disappears or are recognized only at necropsy Usually no treatment is necessary When active intervention is required it is the [illegible]

to the excretion of toxic products elaborated during the infection by the *plugging of capillaries with unusually large numbers of* bacteria and the formation of minute emboli and infarcts when unusually virulent bacteria are concerned or by other factors It is sometimes impossible to determine whether renal lesions are due to remote effects of an infection elsewhere in the body or to the immediate action of pathogenic organisms locally in the kidney tissues or to a combination of both factors

The Bacillary Infections —The *colon bacillus* heads the list and is discussed more fully on page 307 During colon bacillus septicemia or involvement of other organs or tissues the kidney may be mildly affected and play a minor rôle in the production of symptoms or may be entirely unaffected *B proteus infections*[40] occasionally occur especially following instrumentation or operation on the urethra or bladder Septicemia has been observed in 17 cases of which 5 died During typhoid fever B typhosus may produce miliary abscesses in the renal cortex and medulla Symptomless bacilluria is common If obstruction occurs pyonephrosis results Both kidneys are usually involved Numerous reports have been gathered by Patch[45] who adds 2 cases of his own Christeller[13] regards the lesions as typical Typhus Knotchen *Tubercle bacillus* infection of the kidney is discussed on page 315 Gregerson and Lund[27] and Wohlwill[59] found microscopic areas of specific granulation tissue and inflammation in the kidneys due to Brucella melitensis during undulant fever Several cases of pyelonephritis due to *B dysenteriae* are reported by Calalb[13 40a] Jean[32] records a case of *anthrax* of the kidney with perinephritic abscess Because of the massive bacteremia which occasionally occurs in anthrax the kidney capillaries contain myriads of bacilli which may produce lesions by mechanical obstruction alone The specific lesions of *glanders*[13] frequently occur in the kidney during the infection Schottmuller[13] reports 2 cases of *gas bacillus* infection in which many of the renal vessels especially in the glomeruli were plugged with bacilli The tubules were filled with debris and bacilli were found in the urine Metastatic lesions may occur in the kidneys during *plague*[13] and probably in *tularemia* Miller and Branch described infarcts in th
cytes around many gl
kidneys are commonly
invasion of the vibrios
in the kidneys In leprosy[13] the kidneys in rare cases are infiltrated with leprous nodes and tissue Myriads of bacilli may be present and escape into the urine

The Coccal Infections —The *staphylococcus* because of the frequency with which it invades the blood stream is the commonest encountered The kidney is the chief site involved in certain cases as described on page 313 Frequently it is one of many organs or sites involved in widespread metastatic invasions Joyce[35] states that of 61 cases of staphylococcal infection renal lesions occurred in 14 Because of the cortical location of the abscesses there may be little or no evidence c ... the lesions are found only at necropsy
hemolyticus are of two g
kidney by the toxic products of growth which give rise to glo

nephritis, described at length in Chapter XXI, and (*b*) by direct invasion of renal tissue and abscess formation Seven cases of streptococcus infection of the kidney are described by Cabot and Crabtree[17] The kidneys were often enlarged Abscesses were usually multiple and were present in varying stages of development. They were found scattered in the cortex and medulla Thrombi containing chains of cocci were found in various portions, often

There was a focal reaction in the cortex and medulla, but no definite bacterial emboli were found after twenty four hours Cocci appeared in the urine Strang and Semsroth[24] report acute endarteritis and destruction of the intima of the renal arterioles probably caused by Streptococcus viridans septicemia In subacute bacterial endocarditis associated with Streptococcus viridans bacteriemia,[2] diffuse glomerulitis, embolic and focal glomerulitis occur in a high percentage of cases Streptococci lodge in the capillaries and cause hyaline and fibrous changes Bell[12] believes that necrosis of the glomeruli is probably a toxic effect rather than the result of infarction Clawson injected streptococci into the blood stream and noted that inflammatory lesions of low intensity developed about the masses of cocci which were deposited in the kidney The importance of infected teeth and tonsils as foci of infection of Streptococcus viridans infection has been greatly exaggerated Lesions produced by the *gonococcus* have been discussed on page 320 The *pneumococcus*, like the hemolytic streptococcus, may affect the kidneys in different ways first as a result of the excretion of toxic

meningitis, multiple kidney abscesses and perinephritic abscess due to pneumococcus Type III

The kidneys were enlarged and boggy The surfaces were irregular, due to the bulging of numerous abscesses On section, innumerable

were necrotic and contained polymorphonuclear leukocytes They were surrounded by a zone of inflammation Focal and diffuse areas of leuko-

varying degrees of degeneration During the illness no abnormalities of the urine other than those found in acute infection were present

Castaigne reported a case of renal abscess due to M tetragenus

The Filtrable Virus Infections —Hemorrhagic nephritis may occur as a result of direct action of the virus of *varicella*[13] In *smallpox*[13] Weigert found small foci of specific lesions in the kidney Fahr reported small round cell infiltrations in *measles*[13] In *yellow fever*[41] engorged glomeruli dilated tubules hyaline and granular degenera

rhages in the pelvis and intranuclear inclusion bodies in the cells of the tubules in 50 per cent of cases at necropsy The urine during life occasionally contained albumin pus erythrocytes and casts The non protein nitrogen of the blood was occasionally increased It is uncertain whether the changes found were associated with encephalitis or were merely secondary in nature

The Spirochete Infections —Syphilis of the kidney is discussed on page 319 The kidneys are frequently affected in *relapsing fever*[13] Masses of spirochetes may be found in the renal vessels *Weil's disease*[13] (*infectious jaundice*) almost always affects the kidneys They are often doubled in size and show hemorrhages inflammation and cellular infiltration

eterized urine Other cases are reported by Fischer

and filaria embryos may abound in the kidney cortex and medulla Marked fibrosis and parenchymal degeneration occurs *Echino-*

produce typical colonies and granulomatous changes

cosis has been discussed *Blastomycosis streptothricosis sporo-*

involve the kidneys

nilia are found in the

The lesions of each

7 SUTER, F 1931 Die infektiosen, nichttuberkulösen Erkrankungen der Niere und oberen Harnwege, Handb d inn Med, v Bergmann and Staehelin, 6, Pt II, 1877-1897
8 Young's Practice of Urology 1927 Vol 1

Special Articles

9 BEACHAM, H T 1933 Specificity of Pathogenic Infections of the Kidney, J Urol, 29, 197-215
10 BECKMAN, K, AND VAN DER REIS 1924 Zur klinischen Bakteriologie und Therapie der Pyelitis und Cystopyelitis, Ztschr f klin Med, 101, 229-244
11 BEER, E 1929 Diagnosis and Treatment of Chronic Renal Tuberculosis, Am J Surg, 7, 607-616
12 BELL, E T 1932 Glomerular lesions associated with endocarditis, *Am J Path*, *8* *639-664*
13 v BERGMANN, G, AND STAEHELIN, R 1925 Handb d inn Med, vols 1 and 2
14. BITTER, L, AND GUNDEL, M 1925 Ueber die Bedeutung der Typen fur den Verlauf von Colipyelitiden, Klin Wchnschr, 4, 1395-1396
14a BLAISDELL, J L 1934 Renal lesions of rheumatic fever, Am J Path, 10, 287-299
15 BOOK, M H 1933 The permeability of the kidney to bacteria, Am J Path, 9, 569-596

277-294
25 FISCHER, W 1920 Die Amoebiasis beim Menschen, Ergebn d inn Med u Kinderh, 18, 30-108
26 GOHRBANDT, P 1926 Histologische Untersuchungen über die Beteiligung des Nierenbeckens bei Erkrankungen der Niere, Arch f path Anat u Physiol, 259, 269-290
27 ... AND ... T M 1931 De Patologisk-anatomiske ... lstidende, 74, 349-358
... J 1930 Ascending infection of ... 33-249
... *kenntnis der Staphylokokken* ... 280
... 1925 The kidney a filter for bacteria, Am J Dis Child, ...
31 HINMAN, F 1932 Urinary infections their classification, Calif and West Med, 36, 1-6
32 JEAN, M G 1929 Anthrax d un rein en ectopie pelvienne, J d urol, 28, 101-103
33 JOHNSON, F P, AND HILL, J H 1924 Gonococcal infection of the kidney and criteria for its diagnosis, J Urol, 11, 177-187
34 JONES, F S, AND LITTLE, R B 1926 The organism associated with specific infectious cystitis and pyelonephritis of cows, J Exper Med, 44 11-20

35 JOYCE, J L 1930 A study of staphylococcal disease the renal cases Guy s Hosp Rep 80 169–193
The pathologic changes in pyelitis of children

42 MEDLAR E M 1926 Cases of renal infection in pulmonary tuberculosis Am J Path 2 401–413
42a MONTGOMERY L G AND ALLEN R B 1934 Tuberculous bacilluria Am Rev Tuberc 30 92
43 NESBIT R M 1932 Acute staphylococcal infections of the kidney J Am Med Assn 98 709–714 (references)
43a PALILOV V G 1934 Rheumatic infection of the kidney Klin Med (Moscow) 12 1031 1078

199–221
46 PAWAN J L 1926 Case of pyelitis associated with Entamoeba histolytica Ann Trop Med 20 199–200
47 QUINBY, W C 1932 Observations on the physiology and pathology of the ureter J Urol 7 259–270
48 REICHE F 1926 Zur Pathogenese der Pyelitis acuta Med Klin, 22 1838–1840
49 RICH, A R 1932 Pathology of nineteen cases of a peculiar and specific form of nephritis associated with acquired syphilis Bull Johns Hopkins Hosp, 50 357–382
50 ROSENBUSCH H 1929 Die Beteiligung der Nieren bei den Pyelitiden der Kinder Jahrb f Kinderh 125 127–159
51 SCOTT W W 1929 Blood stream infections in urology J Urol 21 527–566
52 STENHOUSE H M 1925 Renal pathology in Filariasis bancrofti, U S Nav Med Bull 22 1–12
53 STOECKENIUS W 1912 Beobachtungen an Todesfallen bei frischen Syphilis Beitr z path Anat u z allg Path 68 185–212
54 STRANG J J AND SEMSROTH K 1931 Streptococcic septicemia with vascular lesions Arch Int Med 47, 583–592
55 WAY J K G 1928 Renal abscess following gonorrhea Brit Med J 1 716
56 WESSEL E 1933 Pathologisch-anatomische Statistik der infektiosen Erkrankungen der Harnorgane einschliesslich der Tuberkulose Ztschr f urol Chir 38 23
57 WILDBOLZ H 1929 Renal tuberculosis J Urol 21 145–179
57a ——— 1934 Significance of occurrence of tubercle bacilli in urine, München med
58 WILSON
acute pyelitis
59 WOHLWIL
Arch f path Anat u
60 WINSBURY WHITE H P 1933 The spread of infection from the uterine cervix to the urinary tract and the ascent of infection from the lower urinary tract to the kidneys, Brit J Urol 5 249–267

CHAPTER XXI

INFECTION BY STREPTOCOCCI IN RELATION TO RECOVERY AND PROGRESS IN NEPHRITIS *

By WARFIELD T LONGCOPE M D JAMES BORDLEY III M D

AND

FRANCIS D W LUKENS M D

***Introduction* Previous Evidence of Hemolytic Streptococci as a Factor in the Etiology of Glomerular Nephritis** —It is now recognized that the onset of acute glomerular or hemorrhagic nephritis is usually preceded or accompanied by an acute infection (Loehlein [5] Fahr [16] Volhard [53] Bell Clawson and Hartzell [8] Kollert [28] Fishberg [17] Munk [43] Gray [9] Lichtwitz [30] Longcope [34 35] Van Slyke [52] Addis [1 2 4]) Scarlatina tonsillitis severe pharyngitis sinusitis and bronchitis are the forms of infection which are most frequently observed It is well known too that these infections are frequently caused by hemolytic streptococci and therefore the view has been widely adopted that hemolytic streptococci are intimately connected with [illegible] Th[illegible] of the [illegible] course of acute or subacute glomerular nephritis serve to uphold this idea

Bacteriological studies have now been made of the infections found in 87 of 92 cases of acute or subacute glomerular nephriti † In all but 3 cases some definite infection usually of the upper respiratory tract was obvious Cultures made from the infections in 11 of these 87 patients did not show an organism that could be held responsible for the infection Satisfactory information could be obtained however concerning the infecting organism in a total of 76 cases In 72 of these the infection was associated with hemolytic streptococci of some type In 6 of the 72 cases there was in addition an infection caused by some other bacteria A cystitis due to gonococci occurred in 2 of these lobar pneumonia

* Aided by a grant from the Ella Sachs Plotz Foundation

† Since this paper has been written a number of additional cases have been observed Except in a few particulars the studies that have been made on these new cases confirm the observations recorded in this paper

due to pneumococcus Type II occurred in 2, a sinusitis due to pneumococcus Group IV in 1 case. It was presumed that the infections in 66 cases were caused exclusively by hemolytic streptococci.

Of the remaining 4 patients from whom hemolytic streptococci were not cultured, 1 had scarlatina, 1 suffered from a sinus infection due to pneumococcus Group IV and 2 had bacterial endocarditis due to Streptococcus viridans. It is interesting to note that rheumatic endocarditis, causing mitral stenosis and insufficiency, was present in five of the 76 cases.*

Bacteriological examinations such as this furnish, perhaps, only indirect evidence that hemolytic streptococci are related etiologically to glomerular nephritis. There is, however, considerable corroborative evidence which might support this idea. There seems to be little question for instance that diffuse glomerular nephritis as well as the so-called focal form of the disease, may occur as a complication of bacterial endocarditis caused by Streptococcus viridans. Two such cases quite typical in their pathological character were observed in this series while Baehr and Lande[7] state that diffuse glomerular nephritis was noted in 11.5 per cent of their series of 77 cases of bacterial endocarditis. Furthermore, it has been shown that the skin of a large proportion of patients suffering from acute and subacute glomerular nephritis is much more sensitive than is the normal skin to culture filtrates of hemolytic streptococci of β type (Longcope[23]) or to the proteins derived from these organisms (Derick and Fulton[14]). We have also found that the serum of these patients will agglutinate killed cultures of a limited number of strains of hemolytic streptococci of β type. Care was taken to kill the organisms by heat before the agglutination reactions were performed, in order to obviate confusion with the interesting, non-specific agglutination of living cultures of hemolytic streptococci, described by Tillett and Abernethy.[60] Clawson and Wetherby[12] have stated that they could demonstrate agglutination of streptococci with high dilutions of serum from cases of acute nephritis, while Seegal, Heidelberger and Jost[48] refer to the fact that the serum from cases of acute nephritis causes precipitation of the nucleoprotein from hemolytic streptococci of β type.

In the last three years a number of observations have been made



* ... considered as a diffuse nephritis

by Dr Allan and one of the authors (W T L) upon the antistreptolysin content *of the serum in cases of nephritis during* the acute and chronic stage of the disease In a number of instances the antistreptolysin content of the serum is greatly elevated during the acute stage of the disease and in a few it is found to be high *during the* subacute stage of the disease The observations have not yet progressed far enough to show whether the antistreptolysin content of the serum bears any relation either to the course of the infection by hemolytic streptococci or to the course of the nephritis Such observations as those cited suggest that during the acute and subacute phases of glomerular nephritis the patient may respond abnormally in several ways to hemolytic streptococci or to the proteins of this organism

There is now in addition experimental evidence to indicate that both hemolytic and non hemolytic streptococci may cause under certain conditions a diffuse glomerulitis in rabbits The histological lesions produced in this manner imitate very closely the pathological picture of glomerular nephritis in man A discussion of the literature upon experimental glomerular nephritis and descriptions of experiments is to be found in a previous communica*tion (Lukens and Longcope*[38]*) and in an article by McLeod* and Finney[40] In the first series of experiments killed cultures of hemolytic streptococci of β type were injected into the left renal artery of a series of normal rabbits and of a series of rabbits sensitized *to hemolytic streptococci of β type Diffuse glomerulitis* occurred in only 2 5 per cent of the normal rabbits subjected to intra arterial injections of hemolytic streptococci but in 73 9 per cent of the sensitized rabbits It was therefore concluded that sensitization or infection of the animal rendered *the kidney in some* way particularly susceptible to the action of the dead bodies of the hemolytic streptococci which were brought into direct contact with the glomerular capillaries McLeod and Finney have varied these experiments by using killed cultures of Streptococcus viridans They have found that suspensions of these bacteria in salt solution injected into the left renal artery also cause at times the most

h d ff ence n the s scepti

as

It

ed

es

quite

in all

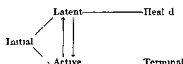
They

sensitized animals between the intensity of the skin react of the presence of eye reactions and the occurrence of glomerulitis Lukens[37] was able to produce somewhat similar lesions in the kidneys of a limited number of normal rabbits by making the injections

of killed hemolytic streptococci into the left renal artery of the same rabbit at weekly intervals It seems therefore to be definitely established that a form of acute glomerulitis, reproducing closely the histological picture of acute glomerular nephritis in man can be obtained experimentally in rabbits The exact mechanism that is responsible for the inception of this glomerulitis is not, at the present time clear

Although it is possible that bacteria other than streptococci such as pneumococci may be responsible for the onset of acute

importance to establish beyond the shadow of a doubt the etiology of glomerular nephritis but it is also necessary to understand more precisely the conditions under which the disease is initiated, the method of recovery and the reasons for progression to a chronic stage or to a fatal termination The elaborate and exact studies of Volhard of Van Slyke and his collaborators and of Addis have shed much light on the natural history of the disease The diagram which Addis uses to indicate the various stages of the disease is shown below



The method too which he has devised[3] for obtaining quantitative estimations of the amounts of albumin and formed elements excreted in the concentrated urine over a period of twelve hours has proved of much value The method has been employed in many cases which will be presented later The urea-clearance test devised by Van Slyke etc has been of much value in estimating the degree of impairment of renal function

The clinical course of hemorrhagic Bright s disease is varied During its progress the dominant features of the illness may change in such a remarkable manner that from superficial examination the different stages may seem to bear few resemblances one to another The complete picture must usually be pieced together from information obtained from observation made over comparatively short periods of the patient s illness It is the initial or acute phases and the terminal stages that are most familiar Less is known about the intermediate stages of the disease though the important clinical descriptions of Volhard Addis and Van Slyke have done much to elucidate this phase and thus bridge the gap

It is now recognized that the familiar acute or initial stage may be

glomerular nephritis It is seen most frequently during the course of an acute infection In all probability *the instances of benign*

that, in some instances, the symptomless initial stage may progress to a latent phase, and later to the typical chronic form of glomerular nephritis In occasional instances the amounts of albumin, of red blood cells and of casts, which are found in the urine of these patients with an insidious onset, but without other symptoms or signs, are in all respects the same as those found in patients with an acute onset attended by the marked hypertension anasarca, *nausea and vomiting characteristic of the onset of severe acute* hemorrhagic nephritis Indeed, there is less and less tendency to attempt to distinguish, on clinical grounds alone, a focal form of glomerular nephritis Addis takes this point of view, and the authors have finally found it impossible to differentiate from clinical examination the two varieties of glomerular nephritis Therefore, they have included for practical purposes, those patients with extremely mild onset as well as those with violent onset in this series of cases of acute hemorrhagic Bright s disease The authors have not, however included a number of patients in this series who, incidental

or duri

to show

only fo

as has been pointed out by Rylin and by Blue, are not all

nephritis such as those recorded by Loeb,[31] by Goldring[18] and by Coburn,[13] have not been encountered by us during the acute stages of rheumatic fever

Following the acute, or initial stage, the disease may progress, as is well known, in a variety of ways Rapid and complete recovery *may ensue, or the patient may become symptomless and the renal* functions normal, but for weeks or months there may be albumin, casts or red blood cells in the urine This latent phase may end in recovery, change later to an active or, as Volhard designates it, a nephrotic stage, or may progress without this variation in symptoms, after months or years, to the terminal phase In many

instances the initial stage runs imperceptibly into the active nephrotic or subacute phase After weeks or months the active stage may be replaced by a latent phase resulting occasionally in recovery but more often terminating fatally A few patients die in the acute attack Others progress rapidly from the initial to the active stage and die within a few weeks or months with massive edema hypertension and hematuria

It can readily be appreciated from this brief outline that hemorrhagic Bright s disease may pursue an extremely varied course Unrecognizable at one time except by careful examination of the urine simulating closely in some patients a nephrosis it reproduces in others particularly in the terminal stages a clinical picture of vascular nephritis or nephrosclerosis It is only when one has followed the entire course of the disease from beginning to end that one can gain an accurate conception of the natural history of glomerular nephritis

Plan of the Present Experiments —Although much has been done to clarify this important part of the problem there still remains considerable uncertainty regarding the factors that are responsible for recovery or which determine an unfavorable progress In an effort to shed some light on this important matter the authors have followed with considerable care a total of 72 cases of hemorrhagic nephritis The disease developed in 7 instances under [illegible]

[illegible] in a few instances whether the disease was in the late period of the initial stage or in the early period of the active phase It is possible that 1 or 2 patients were in the latent stage when they were first seen Observations have been made continuously or at intervals of a few months in this series of 72 patients for periods varying from one to nine years or until the death of the patient Patients who have recovered completely have subsequently been examined at intervals of six months to one year In addition to the clinical examinations with cultures from the pharynx determinations of the renal function have been made by the estimation of the phthalein excretion by determining the concentration and dilution of the urine by the non protein nitrogen of the blood and [illegible]

grouped according to the classification of Addis into those who have recovered those who are presumably in the latent stage those who are in the active or terminal stage and those who have died Twenty six patients have recovered 7 of these have been followed

for from seven to nine years 4 from five to seven years 5 from three to five years 7 from one to three years and 3 for less than one year

studied for from five to eight years 5 from two to five years and 2 from one to two years Twenty two patients have died In 3 of these patients the disease lasted for from three to five years in 4 from one to three years in 5 from six months to one year in 7 for less than six months and in 3 for less than two weeks The fatal cases included two examples of subacute bacterial endocarditis due to Streptococcus viridans and 3 patients who died during the first two weeks of their illness One of them had an extensive infection of the throat and cervical lymph nodes due to hemolytic strepto cocci associated with pneumonia 1 patient had erysipelas and 1 patient suffered from pansinusitis caused by hemolytic streptococci

Factors Determining Outcome of the Initial Attack —(*a*) **Severity of the Attack.** —*Continuous study of many patients from the initial* stage to recovery or through the protean manifestations of the disease to death indicates that there may be several factors which have bearing on the outcome of the disease It is questionable as to whether the actual severity of the acute attack plays an impor tant part in the eventual recovery for in some patients who recover completely the acute phase is characterized by severe symptoms with considerable edema hypertension oliguria marked hematuria and albuminuria and a measurable impairment of renal function while in others who progress to the latent active or terminal stages of the disease the symptoms at onset are mild the initial edema in significant and the renal functional tests practically within normal limits *The hematuria may be slight but usually* the albuminuria is marked

Though the severity of the acute attack of nephritis in the initial stage of the disease does not seem to be of paramount importance ... recover the

reaction to the acute infection was sharp with a rise in tempera ture and with evidence of intoxication though the acute attack of nephritis might be alarmingly severe convalescence was often rapid and recovery quite prompt In a careful analysis of these cases they have found that a very large proportion of cases of nephritis which eventually have recovered *completely* were ushered in by

an infection with severe constitutional symptoms On the other hand, most of the cases which progressed to a chronic stage, and often resulted in death, were associated with mild chronic streptococcus infections which usually affected the tonsils or the paranasal sinuses In these patients, constitutional symptoms from the infection were mild and sometimes the infection could not have been discovered unless careful examinations of the sinuses had been made

(*b*) **Duration of the Acute Attack** —The prolongation of the acute phase, with persistence of edema and the continuation of marked *albuminuria, also seems to influence the eventual outcome When* these features of the disease continue without abatement, or recur during the period of expected convalescence, progress to the active stage is common, and the probability of recovery much reduced It may be seen from Table 30 that all but 2 of the patients that recov-

TABLE 30 —DURATION OF SYMPTOMS BEFORE OBSERVATION

Condition	Total cases	Under 1 month	1 to 6 months	Over 6 months.
Well	26	24	2	
Latent	14	10	3	1
Active	10	6	3	1
Dead	22	6	13	3
Total	72	46	21	5

ered came under observation during the first weeks of the disease, [illegible]

determine with accuracy the termination of the acute or initial stage, but an effort has been made to do this for the patients who have recov- [illegible]

estimate the duration of the acute phase Table 31 shows, however,

TABLE 31 —DURATION OF INITIAL STAGE OR ACUTE ILLNESS

Condition	Total cases	Under 1 month	1 to 3 months	3 to 6 months
Well	*26*	*11*	*11*	4
Latent	14	1	8	5
Active	6	0	2	4

that in those patients who have recovered, convalescence was almost uniformly established within three months from the onset of the disease, and in about one-half of them this took place within one month On the other hand, in only 1 of the 14 patients who are now in the latent stage was convalescence established within one month, and in 5, convalescence was not established within three

months of onset In most of the 6 patients now in the active stage of the disease in whom some rough estimate could be made of the duration of acute symptoms there was no amelioration of these symptoms before at least three months had elapsed

(c) **Persistence of Infection** —A matter which seems to influence directly the favorable or unfavorable outcome of the acute attack is the persistence of infections In *previous communications* evidence was presented to show that the progress of acute or sub acute nephritis is quite closely connected with the disappearance *or persistence of the primary infection or of the bacteria responsible for the infection* This suggestion is reasonable if it can be demonstrated that the onset of the acute nephritis is directly connected with the primary infection Under these circumstances it might follow that elimination of the infection or of the infecting organisms would remove the focus which elaborated continuously or intermittently some substance injurious to the kidney On the other hand persistence of the infection or of the infecting organism might result in progression of the nephritis to a chronic state or to death

(d) **Relation of Recurring Infections to the Progress of the Disease** — Though there is general agreement that acute infections usually

infection or through its elimination Clausen[1] has noticed that the symptoms of the acute nephritis are prolonged by persistence of the infection *Only 1 of his 25 children in whom recovery or* rapid improvement occurred within four weeks of onset showed persistence of the primary infection whereas 33 of the 43 cases in whom the symptoms continued for from four weeks to two years had chronic infections Lyttle and Rosenberg[38] also comment on the persistence of infections in their patients who progressed to a chronic stage of the disease Platt[44] concludes that the course of acute nephritis is favorably influenced by the removal of foci of infection while Gray [9] in a study of acute subacute and chronic glomerular nephritis suggests that the progress from the acute to the chronic state depends upon the persistence of an infection Guild[22] on the other hand could not determine that the *persistence or exacerbation* of infections influenced unfavorably the eventual outcome of acute attacks of nephritis which occurred *in 34 children* Her examinations were made in 18 cases after an interval of less than five years and in 16 cases after an interval of five years or more Volhard as well as Van Slyke questions the *importance that can* be attributed to the persistence or exacerbation of infections in prolonging the course of the acute attack of nephritis or in influencing its outcome Both Van Slyke and

Addis however recognize the frequency of exacerbation of symptoms during the initial stages of nephritis, following operative procedures or recurrences of infection, but Addis has so rarely

effort was made to eliminate the infections about the throat and paranasal sinuses Tonsillectomy was performed in many cases, while a few patients were subjected to radical sinus operations During the repeated observations which have been made on these patients over a period of from one to nine years, cultures have been obtained at fairly frequent intervals either from the persistent infection or from the region which was the seat of the original infection This latter procedure has proved to be of importance, for in several
has persisted f
the course of

cases in an attempt to combat the infection

One point which adds weight to the idea that the activity of the infection influences the renal lesion is the frequent but often fleeting exacerbation of the nephritis following surgical interference with the infection during the initial stage of the disease or in the course of convalescence This has occurred repeatedly in the authors experience as it has in the experience of others The authors have not considered however, that serious or permanent harm has resulted from these transient exacerbations On the other hand it has appeared that natural recrudescences of the infection by streptococci have been directly related particularly during the initial stage of the disease, to more severe and prolonged exacerbations of the acute symptoms which have had a deleterious effect

week to week and unless the exacerbation of the infection attracts particular attention and the increase in symptoms of the nephritis is severe it is difficult to convince oneself that there is any connection between the two One rarely can detect as Addis has pointed out a pronounced increase of symptoms during the latent stage

when exacerbations of infections occur The experience of the authors has been the same when the patient is in the terminal stage of the disease An exact analysis of the data now available on the relation of infections to the progress of hemorrhagic nephritis in a much larger series of cases than was originally described will shortly be published by McLeod Winkenwerder and Baker but in the meantime some reference can be made to the results of their studies

(*e*) **Latent Period Between Infection and Onset of Nephritis** — It has been interesting to observe the latent period between the onset of acute streptococcus infection and the onset of the acute nephritis This as has been generally recognized covers a period of from one to three weeks Osman Close and Carter[46] quote Goodall and Turner who state that the appearance of nephritis following scarlet fever comes mainly between the eleventh and thirty fifth days after the onset of scarlet fever with a maximum incidence about the twentieth day Osman Close and Carter however think that the interval between the attack of streptococcal tonsillitis and the onset of acute nephritis is much shorter than it is in scarlet fever The mean time of onset in 37 post tonsillitis cases was ten days The statistics which Winkenwerder McLeod and Baker[54] have collected show that the time of onset following streptococcal tonsillitis or acute streptococcal infection of the upper respiratory tract compares very well with the figures of Osman Close and Carter In the 41 cases recorded by Winkenwerder McLeod and Baker[54] the onset of the acute nephritis appeared on the third to the twenty-eighth day the average interval being eleven days It has been interesting to find however that the onset of the acute exacerbation in nephritis following tonsillectomy or the flare-up of a streptococcus infection is much shorter than this Gross hematuria and marked albuminuria may occur within twenty four hours after the rise in temperature associated with the flare-up of an infection Following tonsillectomy or after a radical operation on the sinuses a noticeable increase in blood albumin and casts in the urine has been observed within six to eight hours of the operation In the serious exacerbations of nephritis edema of the face and rise in blood pressure may be observed within twenty four hours after the onset of infection or following operation

Infections by β hemolytic streptococci in patients who have recovered completely from acute nephritis have not on the other hand been attended by recurrence of the signs or symptoms of nephritis Several of our patients who have recovered have subsequently experienced severe infections of some sort due to hemolytic streptococci and during the course of this illness there has been no evidence of an exacerbation of chronic or latent nephritis and no indication of the onset of a second attack of acute nephritis

Although sufficient data have not yet been collected from which one could draw conclusions such experiences suggest that the patient who has once recovered from an attack of acute hemorrhagic nephritis is no longer susceptible to a recurrence of the disease when he contracts an infection due to hemolytic streptococci Patients who have recovered from hemorrhagic nephritis may also become pregnant and proceed normally to term without the recurrence of any of the symptoms or signs of nephritis This has occurred in 3 of the authors patients

As one studies the progress of the disease in these patients with hemorrhagic nephritis from the onset to recovery or death and as one follows the course of the infections in these patients one is impressed with the close relationship which one process bears to the other In the final analysis one is forced to the conclusion that glomerular or hemorrhagic nephritis is actually one form of an infectious disease This is its essential character In certain respects it is analogous to rheumatic fever If one substitutes the kidney for the heart the two diseases have much in common The initial stage presents all the characteristics of an acute infection Sometimes it is in extremely mild form but usually it is of varying degrees of severity Complete recovery from the acute attack does not seem to leave the patient liable as does an acute attack of rheumatic heart disease to subsequent attacks of the disease On the other hand progression to the chronic stage of hemorrhagic nephritis resembles in many ways a persistent infection in which the kidneys suffer continuous damage in somewhat the same manner as the heart suffers continuous damage during repeated exacerbations of rheumatic fever Little by little the functional derangement of the kidneys begins to dominate the clinical picture just as the failing circulation dominates the clinical picture in rheumatic heart disease The complicated and dramatic symptoms of renal failure gradually demand the undivided attention of the physician and in an effort to understand combat and relieve these he is likely to [illegible]

[illegible]

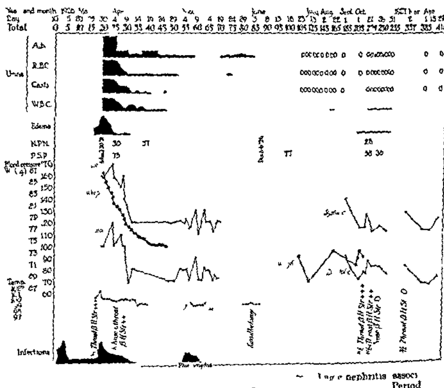
sirable to consider the patients who have been under investigation in more detail To do this they will be discussed in four groups Group I is comprised of those patients who have recovered Group II of those who are in the latent stage Group III is comprised of those in the active stage and Group IV of those who have died

Group I 26 Cases —In 9 of the 26 cases the primary attack was severe [illegible]

[illegible]

was evident Within a few days or at most weeks the pronounced

symptoms subsided, the infection improved and the majority of these patients began to convalesce. In most of these patients, however, even though the infection was eliminated, the urine continued to show small amounts of albumin, casts of various kinds and red blood cells for weeks or, indeed, months before normal conditions were reestablished. Case 1 (Fig. 68) illustrates the course of the disease in 1 of these 9 patients who, after a severe initial attack, recovered quite promptly. Case 3 (Fig. 70) is an



— ... nephritis associ... Period

... prompt subsidence of the ... symp- ... recovery ... well and ... unts of showed no physical ... the urine ... min a few casts and numerous red blood ... ally infected tonsils from which ... occasions ... at the

disease was progressive, but after a period of one year the urine became normal, the tonsils ceased to show hemolytic streptococci, tonsillectomy was performed and for a period of one and a half years the patient has been well as measured by all criteria. In this group of 9 cases the initial stage lasted for less than one month in 2 and from one to three months in 7. The entire course of the disease covered less than six months in 4 and from six months to one and a half years in 5.

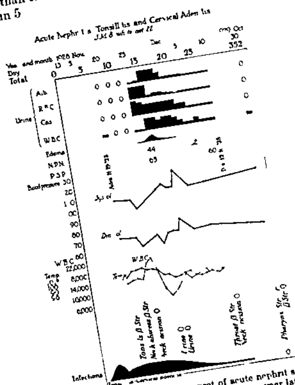


Fig 69 Case 9 S M Showing sudden onset of acute nephritis during observation rapid recovery and normal condition one year later

In 12 of the 26 patients the symptoms at onset were mild and were not accompanied by definite evidence of renal insufficiency, except for the inability to concentrate the urine. The duration of the initial stage was usually short, convalescence prompt and recovery usually rapid. In 2 of these patients the disease developed under observation during the course of an acute infection. In 7 the initial stage lasted less than one month, in 4 from one to three months and in 1 for six months. The entire disease lasted for less

than three months in 3 patients, from three to six months in 4 patients, from six months to one year in 4 patients and for sixteen months in 1 patient It may be seen, therefore, that mildness of onset does not always insure rapid recovery from acute hemorrhagic nephritis, for complete recovery did not take place in 5 of these 12 patients until six months had elapsed from the onset of

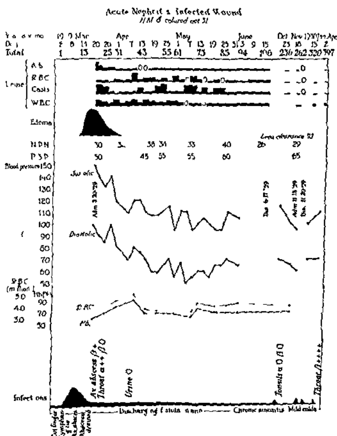


Fig 70 —Case 3 H M Acute nephritis recovery from acute symptoms Excellent physical health with normal tests of renal function but persistence of albuminuria hematuria and cylindruria with presence of β hemolytic streptococci in tonsils Eventual recovery

the disease Case 2 (Fig 69) illustrates, however, the course of the disease in a patient who developed a mild attack of acute hemorrhagic nephritis under observation, and in whom complete recovery took place within three and a half months from the onset. The patient was entirely well at the end of one and a half years, but has since been lost sight of.

In 5 of the 26 patients the onset was insidious and was only detected by examination of the urine Careful examination in 1

and in 1 with scarlet fever In 2 the initial stage lasted for less than one month in 2 from one to three months and in 1 for three and a half months Although the patients were symptomatically well in some cases even before the initial stage had subsided, abnormalities persisted in the urine for from one to three months in 3 cases and for one to two years in 2 cases Reference has already been made to the importance of recognizing this mild form of the disease for the process may advance silently to the long latent stage and finally terminate with the characteristic signs of chronic glomerular nephritis It is well known that some patients who are first seen in the terminal phase of the disease do not give a history of a previous attack of acute nephritis and it is quite possible that in some of these the disease began in the same insidious manner as that illustrated by the course of the disease in the last 2 patients In both of them the acute process was associated with mild attacks of acute tonsillitis due to hemolytic streptococci of β type and in both there were sudden increases of albumin and red blood cells in the urine during the exacerbations of the tonsillitis Both patients have been entirely normal to examination for more than five years

When one compares the course of the infection with the course of the nephritis in this group of 26 patients who have recovered it is found that rapid disappearance or elimination of the infection was usually associated with more or less prompt recovery from the nephritis It was not uncommon however to observe exacerbations of the symptoms and signs of the nephritis following tonsillectomy or with recurrence of the infection These recrudescences of the nephritic symptoms were unlike the primary attack in certain respects In the first place they were usually of mild character Occasionally there was some return of the edema with an elevation of the blood pressure but more often the recrudescence was characterized only by a noticeable increase in the albuminuria the cylindruria and the hematuria In the second place, as had been pointed out above, the recrudescences differed from the primary attack in the time interval that elapsed between the operation or the acute infection and the onset of the nephritic recrudescence It is well known that the primary attack follows the acute infection after an interval of one or two weeks with an average of about ten to twelve days while in some instances the first symptoms of nephritis do not appear until the patient is convalescent from the infection The relapses and recrudescences

in these patients, on the other hand, came almost immediately after the operation or with the earliest symptoms of the infection Gross hematuria has been observed from a few hours to twenty-four hours after tonsillectomy in patients who, previous to operation had had only microscopic blood in the urine Elevation of blood-pressure, slight edema and an increase of the abnormal urinary constituents have been detected within the first twenty four or forty-eight hours of an acute infection The difference, therefore, between the primary attack and the recrudescences in their time relation to the onset of the acute infection, or to the operative procedure, is a matter that is worthy of note

Repeated observations and cultures from 24 of these 26 patients, over a period lasting approximately one to nine years, have shown that 20 have remained free from infections due to hemolytic streptococci, and have shown negative cultures since their recovery Several of these patients have had other forms of infections Many have had common colds, 1 has contracted syphilis 1 or 2 have suffered from transient cystitis caused by B coli and 1 has had a severe infection due to Staphylococcus aureus, about an unerupted wisdom tooth Four patients have either shown a few β hemolytic streptococci in cultures from the pharynx on one or two occasions or have had definite infections due to this organism In 2 of these 4 cases, single cultures from the pharynx showed β hemolytic streptococci many months after recovery A third patient (Case 1) two years after recovery, had a severe attack of bronchitis caused by β hemolytic streptococci She passed through the attack without the slightest evidence of a recrudescence of the nephritis and has continued well for four years The fourth patient, a child who

insidious form during an
aricella, has had enlarged
β hemolytic streptococci

have been cultured on many occasions over a period of four years In spite of the chronically infected tonsils there is no evidence of disease of the kidneys Reference has already been made to the fact that patients, once they have recovered may pass through a severe infection by β hemolytic streptococci without experiencing exacerbations of nephritis

Group II—Latent, 14 Cases—In this group the initial stages of the disease were in general similar to the types described for the ... the onset was severe

stage was protracted, for in 8 patients it lasted for at least one to three months and in 5 patients for three to six months

Twelve of these 14 patients are symptomatically well, and many

are at work All are free from edema or show only traces of dependent edema on some occasions In all of them the blood pressure is normal All show some albuminuria all but 1 have hematuria and many of the patients have a few casts in the urine The Addis counts in 3 are only moderately abnormal The disease which has existed in 3 patients for from three to eight years must be considered as slowly progressive unless one accepts the view that the nephritis may actually heal and yet the kidney bear a defect which allows the passage of abnormal amounts of albumin and formed elements Volhard is inclined to believe that in some patients a persistent albuminuria and perhaps hematuria may be regarded as due to a 'Heildefekt but the study which Addis has made of this important group of latent or quiescent cases makes it seem more probable that many or indeed most of them are progressive and end eventually, sometimes only after many years in the terminal stage In 7 of the 14 cases the disease has lasted for from one to three years Some of these patients seem to be improving steadily and it is still possible that complete recovery may ensue In 3 patients the disease has lasted from nine to ten months and in these it is not possible to predict the eventual outcome In 2 of the 3 it seems highly probable that complete recovery will take place One patient was lost sight of after four months observation

In this group the course of the infection and the results of bacteriological examinations have been irregular The patient who has shown recurring signs of nephritis for eight years has had repeated infections the last an acute tonsillitis due to hemolytic streptococci of β type Following tonsillectomy cultures from the pharynx continued to show β hemolytic streptococci One patient

latent stage has persisted for five years showed hemolytic streptococci of β type on one occasion two years after the initial attack Of the 7 patients who have had signs of nephritis for one to three years 1 has frequently given positive cultures of hemolytic streptococci of β type from the tonsils which have not been removed and 1 showed a persistence of this organism in the pharynx for long periods during convalescence In 2 of the 7 patients hemolytic streptococci have never been isolated even from the primary infection and in the remaining 3 patients cultures made since the acute attack have been persistently negative In the 3 patients in which the disease has lasted less than one year, cultures have been repeatedly negative since the subsidence of the acute attack

The ultimate outcome in this group cannot of course be predicted at present It is a shifting group from which patients are trans-

ferred from time to time to the well group or to the progressive group *

Groups III and IV—Active and Living, 10, Died, 22; Total, 32—In this large group of patients, 22 of whom have died, the disease has pursued an extremely varied course Three patients succumbed during the initial stage of the disease, 2 died with subacute bacterial endocarditis and 6 who were first seen in the active or terminal stages died shortly after admission to the hospital Of the remaining 21 patients, 10 are still living

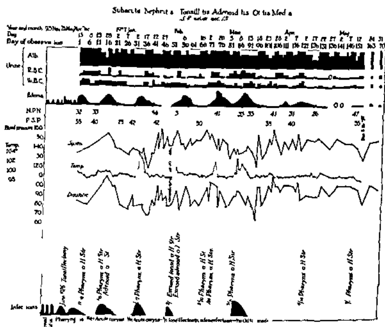


FIG 71 —Case 4 I S Showing prolonged course with mild exacerbations with fever and edema during early stages persistent moderate hypertension almost continuously positive cultures for α hemolytic streptococci from nasopharynx comparatively good health with capacity to work for two and a half years with minimal edema

The description of the progress of the disease in these 21 patients can best be made by dividing them into several types In the *first type of the disease, the acute or initial stage,* which was of varying degrees of severity, ended in a protracted convalescence, often interrupted by exacerbations of acute symptoms Following this long convalescence the patients have been symptomatically well and have often been able to work, but the large amounts of

* Since this article has been written 2 of the cases in this group should be transferred to the well group and 1 to the progressive group

albumin in the urine and the persistence of red blood cells and casts together with some elevation of blood pressure combined with intermittent dependent edema leaves little doubt that the disease is slowly but actively progressive Eight cases belong to this type of which Case 4 (Figs 71 and 72) is a good illustration All of these patients are living and in all of them the disease has lasted for two to seven and a half years The renal functional tests show some impairment in all of the patients in whom it has been possible to make these tests but in Case 4 who has been

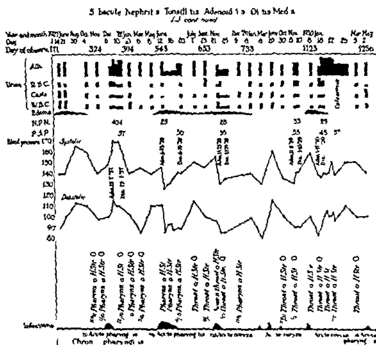


Fig 72 Case 4 I B Continued

under observation for six years the changes are comparatively slight In another patient on the other hand who has been under observation for only two years the phthalein excretion and the urea clearance are both much reduced

In the second type the disease pursued a rapid and rather familiar course In 7 patients the initial stage changed imperceptibly to the active stage which in 4 patients was characterized by massive and uncontrollable edema moderate hypertension and marked albuminuria and hematuria In the other 3 patients the edema

formed a less conspicuous feature, while the hypertension was marked In at least 3, and perhaps 4, of the 7 cases, therefore, the nephrotic symptoms predominated the clinical picture and yet there seemed to be no question that there existed a hemorrhagic or diffuse glomerular nephritis, for hematuria was frequently profuse, the blood-pressure was elevated and the renal function greatly impaired Two of these 4 cases came to autopsy In both there were extensive degenerative changes in the tubular epithelium

and in both of them there were diffuse, though moderate, acute changes in the glomeruli The disease ran a rapid course in all 4 since only 1 patient lived as long as eight months *Indeed in this* entire group of 7 patients the course of the disease was short for 5 of the patients died within a year of onset

In a third group the disease ran a longer and somewhat different course

Two pati

attack of

in which there was pronounced anasarca, moderate hypertension, profuse albuminuria and hematuria. The active phase lasted many months and was characterized by severe exacerbations which were coincident, especially in Case 5, with recurrences of a severe infection of the antrum due to hemolytic streptococci. Following radical operation upon the antrum in this patient there was surprising symptomatic improvement. The edema finally disappeared

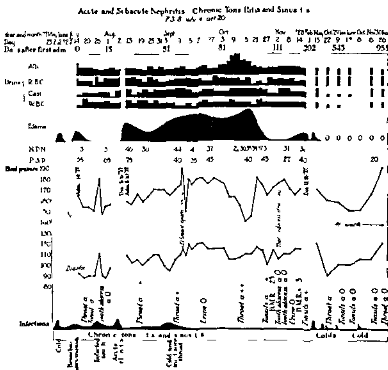


FIG. 14.—Case F. F. S. Showing course of disease from acute stage through nephrotic stage with hypertension to hypertensive stage with complete physical ability for two years. Duration of disease three years.

in both these patients, and for a considerable period before their deaths they were at hard labor every day. With the disappearance of edema the hypertension was more marked and became permanent. This is a sequence of events which has been observed repeatedly by others and to which Van Slyke, in particular, has called attention. The disease then pursued the course which is characteristic of the arteriosclerotic form of nephritis or nephrosclerosis, except for the fact that there was continuous hematuria without

changes in the fundus oculi Throughout the terminal stage the patients felt comparatively well As the disease progressed a yellowish pallor of the skin with anemia became noticeable Both patients died rather suddenly in uremia Autopsy in Case 6 showed extensive chronic diffuse glomerular nephritis with some thickening of the intima of the arterioles of the kidneys There were *no changes in the arterioles of the other organs* In the other

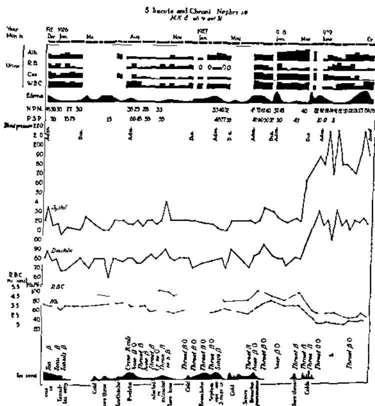


FIG 75 —Case 7 M K Showing course of illness through nephrotic stage to hypertensive stage and death Duration of disease four years

2 cases (7 and 8) the initial attack was comparatively mild, and *for long periods the disease ran the course of a moderately severe* nephrosis without hypertension or measurable evidences of renal insufficiency Shortly before death however, hypertension developed rather quickly the edema disappeared or became much less marked and the disease pursued the course already described for Cases 5 and 6 In Case 7 there were small *colloidal exudates in* the retina In Case 8 there was an extensive hemorrhagic and

exudative retinitis Both of these patients came to autopsy In both patients the kidneys showed (Figs 76 to 78 and 79 to 82) extensive chronic diffuse glomerular nephritis, without changes in the arterioles

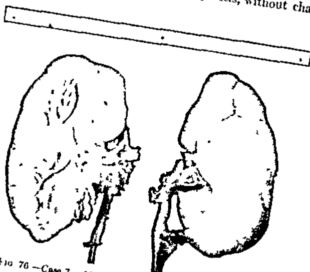


Fig 76 —Case 7 M K Gross appearance of kidneys

...section of the kidney showing glomerular nephritis.

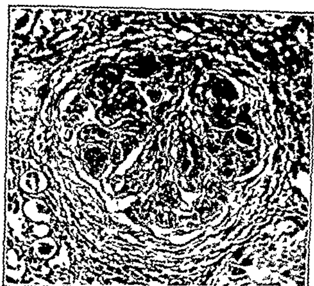


Fig 78.—Case 7 M K High power view of glomerulus

Progress from Acute to Chronic Stage of Glomerular Nephritis

Fig 79 —Case 8 T B Course of disease.



Fig 80 —Case 8 T B Gross appearance of kidney (Bull Johns Hopkins Hosp)



Fig 81 —Case 8 T B Section of cortex showing extensive involvement of glomeruli with old crescent formation adhesions and moderate degree of infiltrations of interstitial tissues. (Bull Johns Hopkins Hosp)

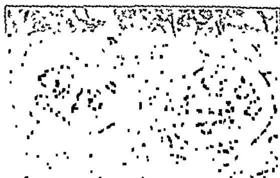
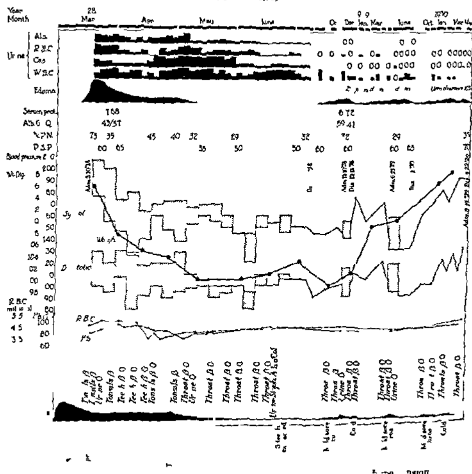


Fig 82 Case 8, T B Higher magnification of two glomeruli (Bull Johns Hopkins Hosp)

The fourth group is representative of a small number of patients who having passed through an attack of acute hemorrhagic nephritis have presented over a period of many years the clinical features typical of essential hypertension Two patients have been



observed in whom the disease has run this course One patient (Case 9) has been under observation for over four years the second patient al o a woman has been under observation for over six years and is symptomatically well She is now working every day

In both patients the initial attack of acute nephritis was rather severe but of comparatively short duration. Both patients have shown for a number of years considerable but irregular elevation of blood pressure and usually faint traces of albumin in the urine. Red blood cells have not been seen in the urine and hyaline casts are rarely observed. The renal function is good in Case 9 and was practically normal in the second cases when tests were made. One patient (Case 9) showed a transient perivasculitis of the retinal vessels during the acute attack of nephritis. The second patient
[illegible]

conclude that patients suffering from essential hypertension may, on rare occasions, survive an attack of acute hemorrhagic nephritis and continue to live in comparatively good health for years afterward.

It is important to determine, if possible, what relation the infections that were observed in this entire group of 32 patients at the onset and during the course of the disease bore to the progress and termination of the nephritis.

In the 3 patients who died during the acute stage there were sever
in 1
roidi
an infection by *Streptococcus viridans* was continuous.

In the 6 cases that died shortly after they were first seen and during the active stage of the disease, 5 showed severe infections either during life or at autopsy; in 2 of them the infection was proven to be due to hemolytic streptococci of β type. Five of the 8 patients of the first type have had recrudescences of infection
[illegible]

able infections of the nasal sinuses due to hemolytic streptococci throughout the course of their entire illness, while 1 patient had recurrent infections due to hemolytic streptococci. Both patients of the fourth type have been free, as far as could be determined, from infections caused by hemolytic streptococci for several years.*

* Case 9 has recently had erysipelas. During the acute illness there was no evidence of an exacerbation of nephritis.

ETIOLOGICAL RELATION OF HEMOLYTIC STREPTOCOCCI TO ACUTE HEMORRHAGIC BRIGHT S DISEASE

In reviewing all the data available at this time bearing on the relationship between the progress of hemorrhagic nephritis and the persistence or recurrence of infection one cannot escape the impression that there exists some connection between the two Although it is possible that this relationship is merely a coincidence such a conclusion seems improbable Reference has already been made to the difficulty of detecting and of completely eradicating the infections of the upper respiratory tract in these patients At times chronic infections of the nasal sinuses have persisted or when they

is in reality a complication of the disease

TABLE 3? —THE COURSE OF NEPHRITIS IN RELATION TO PERSISTENCE OF INFECTION (ONE TO NINE YEARS)

Condition	No of cases	Cultures or infections persistent or recurring: Positive	Negative
Well	?4	4	20
Latent	14	6	8
Progressive active and fatal	32	24	8
	70	34	36

The close connection between infection by streptococci and the

usidered to be in the
ween infections and
ious *

The mortality in this series of young adults is high. This however conforms to the experience of others. Acute hemorrhagic nephritis in children is comparatively benign, but in the adult the disease is much more likely to progress to a latent or chronic state and terminate eventually in death.

Recovery from acute scarlatinal nephritis in children is so common that on surveying the statistics (Fishberg), it appears that unless death occurs during the acute phase of the disease, permanent recovery is the rule. Hansborg[24] examined 284 children, one to ten years after their acute attack of scarlatinal nephritis, and could find no abnormalities in 269. The prognosis seems less favorable, particularly in adults, when nephritis supervenes upon some other form of infection such as tonsillitis. Lichtwitz[10] records 94 cases of nephritis of which 8 became chronic, 3 died and 40 were discharged improved; an immediate recovery from the acute attack in less than 50 per cent. James[27] examined 67 children from three months to fifteen years after an acute attack of nephritis, the average interval being five years. He found that only 9, or 13.3 per cent, had terminated in a chronic form of the disease. Greenwood[20] obtained information concerning the subsequent course of 38 cases of acute and subacute nephritis two to seven years following therapeutic tonsillectomy. Most of the patients were under fifteen years of age. Twenty-three patients were reported in good health, while 10 had progressed to a chronic stage or had died. Clausen[11] reports 73 recoveries from acute or subacute nephritis in 129 children with 20 deaths and 9 cases progressing unfavorably. Aldrich[3] states that of 129 children suffering from acute postinfectious hemorrhagic nephritis 111 recovered, 8 died during the attack, 4 died of other causes, 5 were convalescent and 1 was lost sight of. Lyttle and Rosenberg[33] followed 50 cases of acute glomerular and acute diffuse nephritis in children for at least one year after the primary attack. Of these, 38 had recovered, 6 had died and the remainder progressed to a chronic state. Guild[22] has reviewed the entire subject of the prognosis of acute glomerular nephritis in childhood. Both from the study of her own cases and from those reported in literature she concludes that the outcome is generally favorable.

In the adult, on the other hand, complete recovery seems to be much less common than it is in children. The statistics for cases of Trench nephritis though incomplete in many respects show a surprisingly small number of recoveries. Though Toennessen[44] states that out of 274 cases 68 per cent were discharged from the hospital as recovered, statistics of Hume and Nattrass,[26] Deutsch,[14] Siguret,[41] Magnus-Alsleben[34] and Gross[21] on the outcome of war nephritis in the British, French and German armies show only from 17 to 49.5 per cent recoveries. Schendel examined 120 patients in 1930 and 1931 who had suffered during the World War with war nephritis. Of these, 18 per cent showed residual albuminuria,

varying in age from infants to seventy years as 5 5 per cent They were able to examine 48 of 85 patients from eleven to twenty years after the acute attack Two had died of chronic nephritis 5 were alive but were suffering from chronic nephritis 41 were well This ... recovery rate differed ... ed from the acute ... which there were
20 recovered 21 of the remaining 28 patients over ten years of age recovered which gives a recovery rate of 75 per cent O man[45] studied 56 patients who had had an acute attack of nephritis in childhood or early youth from eighteen months to twenty two years after the attack Of these 61 2 per cent were perfectly well while

does not occur in a very large proportion of cases

In the authors series death has occurred in 22 of 72 cases or in 30 5 per cent and complete recovery in 26 or only 36 per cent Among the fatal cases are included however 2 instances of subacute bacterial endocarditis and 6 patients who were first seen during the late active stage of the disease The criteria for complete recovery have in addition been rigid and it may be that several of the 14 patients now considered to be in the latent stage have in fact recovered from their disease These statistics give therefore only an approximate idea of the severity of the disease and err in all probability on the side of pessimism A few statistics are tabulated below and serve to contrast the mortality in children (Clausen) with that in the adult (Table 33) *

It may well be questioned as to whether the attempts to eradicate infections in this group of 72 patients has resulted in any material benefit to them In many instances it has been impossible to accomplish this with any degree of success but in a number of patients it has seemed that life has been prolonged by constant treatment of the infection or that recovery from the nephritis has occurred when the infection had completely healed and the infective organism had disappeared There are undoubtedly

... been ... rely ... e is ... the ... bed

from the disease

many other important factors that contribute to the ultimate out-

TABLE 33 —PROGRESS OF ACUTE NEPHRITIS

Author	Total cases	Recovery		Latent		Progressive active	
		No	Per cent	No	Per cent	No	Per cent
Hume and Nattrass	281	128	45 5	126	45 0	27	9 5
Deutsch	200	99	49 5	43	21 5	58	29 0
Seguret	47	8	17 0	22	46 7	17	36 3
Magnus-Alsleben	*		40 0		25 0		35 0
Cros	211	94	44 6	46	21 7	71	33 7
Longcope	72	26	36 0	14	19 4	32	44 3
Clausen	10	73	71 5			29	28 5

Conclusions — A description of the course of hemorrhagic nephritis is presented as it was observed in a series of 72 patients who were followed for periods of from one to nine years from the initial or early active stage of the disease

In 26 or 36 per cent of these patients the disease ended with complete recovery in 14 or 19 4 per cent of the cases the acute attack has been superseded by a more or less protracted latent stage in 10 or 3 9 per cent the process is active and either slowly or rapidly progressive and in 22 or 30 5 per cent the disease has sooner or later terminated in death

The relationship of infections particularly of the upper respiratory tract to the onset and progress of the disease is discussed Acute infections caused by hemolytic streptococci were found to precede directly or to accompany the acute attack of hemorrhagic Bright s disease in 72 of 76 patients or in 94 7 per cent Evidence is presented to show that hemolytic streptococci are etiologically related to acute hemorrhagic Bright s disease The disease as it progresses from one stage to another may assume many different clinical forms These variations depend upon several factors but it appears from the clinical and bacteriological studies that are presented that an unfavorable progress is usually connected with exacerbations of the infection due to hemolytic streptococci or to persistence of this infecting organism whereas recovery in the majority of instances is associated with disappearance of the infection or of the hemolytic streptococci

Hemorrhagic nephritis may be regarded as an infectious disease The onset is usually acute During the progressive stages of the

35 per cent presented the picture of a chronic hypertensive nephritis and 47 per cent had progressive chronic nephritis with renal insufficiency. None were apparently perfectly well. McPhee and Kaye give the mortality during the acute attack in a series of 90 patients varying in age from infants to seventy years as 5.5 per cent. They were able to examine 48 of 85 patients from eleven to twenty years after the acute attack. Two had died of chronic nephritis, 5 were alive but were suffering from chronic nephritis, 41 were well. This gives a recovery rate of 85.4 per cent. The recovery rate differed according to the age at which the patients suffered from the acute nephritis. All patients under ten years of age, of which there were 20, recovered; 21 of the remaining 28 patients over ten years of age recovered, which gives a recovery rate of 75 per cent. Osman[6] studied 56 patients who had had an acute attack of nephritis in childhood or early youth from eighteen months to twenty two years after the attack. Of these 64.2 per cent were perfectly well, while 35.7 per cent showed some signs of impaired kidney function, often with evidence of chronic nephritis. The studies of Addis too indicate that complete healing of the lesion in the kidneys in the adult does not occur in a very large proportion of cases.

In the authors' series death has occurred in 22 of 72 cases, or in 30.5 per cent, and complete recovery in 26, or only 36 per cent. Among the fatal cases are included, however, 2 instances of subacute bacterial endocarditis and 6 patients who were first seen during the late active stage of the disease. The criteria for complete recovery have in addition been rigid and it may be that several of the 14 patients now considered to be in the latent stage have in fact recovered from their disease. These statistics give, therefore, only an approximate idea of the severity of the disease and err in all probability on the side of pessimism. A few statistics are tabulated below and serve to contrast the mortality in children (Clausen) with that in the adult (Table 33).*

It may well be questioned as to whether the attempts to eradicate infections in this group of 72 patients has resulted in any material benefit to them. In many instances it has been impossible to accomplish this with any degree of success, but in a number of patients it has seemed that life has been prolonged by constant treatment of the infection, or that recovery from the nephritis has occurred when the infection had completely healed and the infective organism had disappeared. There are undoubtedly

* [illegible] have now been [illegible] 100 cases therefore 40 per cent are in a progressive stage of the disease or ha[illegible] from the disease

many other important factors that contribute to the ultimate out-

TABLE 33 —PROGRESS OF ACUTE NEPHRITIS

Author	Total cases	Recovery		Latent		Progressive active	
		No	Per cent	No	Per cent	No	Per cent
Hume and Nattrass	281	128	45 5	126	45 0	27	9 5
Deutsch	200	99	49 5	43	21 5	58	29 0
S guret	47	8	17 0	22	46 7	17	36 3
Magnus-Alsleben	?		40 0		25 0		35 0
Gros	211	94	44 6	46	21 7	71	33 7
Longcope	72	26	36 0	14	19 4	32	44 3
Clausen	102	73	71 5			29	28 5

Conclusions A description of the course of hemorrhagic nephritis is presented as it was observed in a series of 72 patients who were followed for periods of from one to nine years from the initial or early active stage of the disease

In 26 or 36 per cent of these patients the disease ended with complete recovery in 14 or 19 4 per cent of the cases the acute attack has been superseded by a more or less protracted latent stage in 10 or 3 9 per cent the process is active and either slowly or rapidly progressive and in 22 or 30 5 per cent the disease has sooner or later terminated in death

The relationship of infections particularly of the upper respiratory tract to the onset and progress of the disease is discussed Acute infections caused by hemolytic streptococci were found to precede directly or to accompany the acute attack of hemorrhagic Bright s disease in 72 of 76 patients or in 94 7 per cent Evidence is pre

forms These variations depend upon several factors but it appears from the clinical and bacteriological studies that are presented that an unfavorable progress is usually connected with exacerbations of the infection due to hemolytic streptococci or to persistence of this infecting organism whereas recovery in the majority of instances is associated with disappearance of the infection or of the hemolytic streptococci

Hemorrhagic nephritis may be regarded as an infectious disease The onset is usually acute During the progressive stages of the

infection, the kidneys are more and more seriously involved until in the advanced stages, the symptoms of renal failure dominate the clinical picture

CASE 1 —*Acute nephritis following infection of tonsils and sinuses by* [illegible]

edema decreased and by April [illegible] examination [illegible]

January 1930 patient physically well Examination negative Blood [illegible] no albumin no [illegible] ea clear

[illegible] *t* 400 cc

[illegible] 0 blood [illegible] t normal [illegible] od cells

CASE 2 [illegible]

[illegible] d scarlatina in childhood, occasional [illegible] vo and pleurisy two years ago On [illegible] and [illegible] ck

[illegible] 70

urine cloudy neutral no albumin few leukocytes Cultures from throat show no β hemolytic streptococci

str

co

on

charged June 12 1929

TABLE 34 ADDIS COUNTS

Date	12 hr vol cc	Sp gr	pH	Prot mg per 12 hr p	Red blood cells	Leuko ytes and ep thelium	Casts
Apr 5 19 9	243	1 017	5 0	104 9	136 000 000	22 500 000	1 015 000 (42% rbc cell)
June 6 19 9	301	1 0 0	4 5	86 0	43 200 000	6 300 000	1 140 000 (16% rbc)
Nov 20 1929	460	1 0 0	5 5	66 0	2 06 000	3 000 000	27 000
Oct 1? 1931	?90	1 0?0		20 8	40 000	53 ?00	31 900 (hyaline 100%)

CASE 4 Acute ...

course was charac
rence of edema
and 72 The rec
treated by radium
working regularly

white blood cells 7400 The condition remained practically the same during 1931 1932 and the first part of 1933 She worked daily On March
over sh
cent I
cent nor
globulin
amount
red bloo
1 017

TABLE 35 —ADDIS COUNTS

Date	12 hr vol c	Sp gr	pH	Prot mg per 12 hr p	Red blood cells	Leukocytes and epithelium	Casts
Nov 9 1931	49?	1 013	6 6	1417	?? 140 000	53 054 000	1 10 000
Mar 13 1933	605	1 017	ac	1650	2 400 000	10 600 000	300 500

CASE 5 *Acute nephritis progressing to chronic nephritis and death*

CASE 6 —*Acute nephritis progressing to chronic nephrit s an l death asso ciated with chron c infection of sphenoidal sinus b j α hemol jt c streptococci* (Fig 74) F S Male white aged twenty years Unit No 13197 Admitted August 14 1927 discharged November 16 1927

Chief complaint Swollen bod

Go
no
tw
an
an

ly
bl
hy

Case 8 —Acute nephritis progressing through latent phase to chronic hyper

Autopsy (No 10367) showed chronic glomerular nephritis

Weight 230 pounds Patient has been irregularly at work since October

no β hemolytic
she developed
) for six days
olytic strepto-
cocci was grown from left leg There was no generalized edema The
urine during the acute erysipelas showed specific gravity 1 016 to 1 018

TABLE 36 ADDIS COUNTS

Date	12-h vol cc	Sp g	pH	Prot mg per 12 hr p	Red blood cells	Leukocytes and epithelium	Casts
Nov 7 1931	19	1 0 0	6 6	14	2 [illegible]40 000	10 540 000	23 000
Mar 15 1933	180	1 0 1	ac	[illegible]8	0	2 430 000	0

References

1 Addis T 1925 A clinical classificat on of Bright s d sease J Am Med Assn 85 163 167
2 ——— 1931 Hemorrhagic Bright s disease Bull Johns Hopkins Hosp 49 203 224 271 285

s

I

5 Aldrich C A 1930 Clinical types of nephritis in childhood J Am Med Assn 94 1637 1641
6 Baehr, G 1926 A benign and curable form of hemorrhagic nephrit s J Am Med Assn 86 1001 1004
7 Baehr G and Lande H 1920 Glomerulonephritis as a compl cat on

pen

kins

9a Blackman S S Jr 1934 Pneumococcal lipoid nephrosis and the relation between nephrosis and nepl ritis Bull Johns Hopk ns Hosp 55 85 127
9b Blackman S S Jr Brown J H and Bake G 1931 The pro Bull Johns

23 375–391
itic Med J

29 201 205

193? Streptococcic agglut na and Med 29 566–56
the rhe matic process to the Child 45 933–97?
1 Skin react ons of patients streptococci J Cl n Invest

10 121 138
15 Deutsch F 1921 Kriegsnephritikersch cksale Med Kl n 17 1318 1321
16 Fahr Th 1912 Konnen wir die N erenerkrankungen nach ätio logischen Gesichtspunkten e nteilen? Virchow s Arch f path Anat 210 27? 294
17 Fishberg A M 1930 Hypertension and Nephrit s Philadelphia Lea & Feb ger
18 Goldring W 1931 Occurrence of diffuse glomerulonephrit s in acute rheumatic fever Med Cl n North America, 14 1551 1554
19 Gray J 1928 Causes and sequences in nephritis J Path an l Bact 31 191 213
20 Greenwood E J 1927 Tonsillar seps s and nephrit s Guy s Hosp Rep 77 470–476
21 Gros A 1929 Zur Prognose der akuten Nephritis Munchen med Wchnschr 76 655–657
22 Guild H G 1931 The prognosis of acute glomerular nephrit s in childhood Bull Johns Hopkins Hosp 48 193 ?11
O Brien D P 19 9 and subacute

Prognose ler

n Med Assn

26 Hume W E and Nattrass F J 19?7 The late effects of war nephrit s Quart J Med 21 1–6
27 James R F 1921 The prognosis of nephrit s in cl ldren J Am Med Assn 76 505–508

28 Kollert V Suchanek E and Singer S 1930 Grundlagen der ätiologischen Behandlung der Nierenentzündungen Zentralb f inn Med 51 301 308

1550

32 Loehlein M 1907 Ueber die entzündlichen Veranderungen der Glomeruli der menschlichen Nieren und ihre Bedeutung fur die Nephritis Arbeit aus dem Pathol Inst zu Leipzig, Marchand I

33 ——— 1910 Ueber Nephritis nach dem heutigen Stande der pathologisch anatomischen Forschung Ergebn d inn Med u Kinderheilk 5 411–458

34 Longcope W T 1929 The pathogenesis of glomerular nephritis

46 Osman A A Close H G and Carter H 1933 Studies in Bright s disease VIII Observations on the etiology of scarlatinal nephritis Guy s Hosp Rep 83 360–386

nischen Nephritis
I 173 423–435
1932 Precipitin
Proc Soc Exp

16 845 (Quoted

ological reactions with hemolytic streptococci in acute bacterial infections Bull Johns Hopkins Hosp 50 270–286

eln vol 6

51 Winkenwerder McLeod and Baker To be published

CHAPTER XXII

A COMPARISON OF BLOOD-PRESSURE IN MEN AND WOMEN A STATISTICAL STUDY OF 5540 INDIVIDUALS

By MACNIDER WETHERBY, M D

Introduction.—This study concerns itself with the relative frequency of elevated blood-pressure among men and women The basis for the study is formed by systematic observations upon 5540 individuals 2282 men and 3258 women These individuals were all seen in the out-patient service of the University Hospital, University of Minnesota, during the three-year period from December, 1926, to December, 1929 The material has been subjected to the standardized mathematical analysis applicable to a material of this kind In the course of the analysis certain results were obtained, lending themselves also to a brief additional discussion of normal blood-pressure

As an introductory remark the statement seems justified that among the different phases of blood-pressure which have been the subject of study the pressure of young adults has been most thoroughly and satisfactorily investigated The greatest interest no doubt has been given to the relation of blood-pressure to age, while the relation to sex has been relatively neglected MacWilliam,[12] in his review, summarizes the general concept by stating that most observers report the pressure in women, at least in the first half of life, as 8 to 10 mm lower than in men, Symonds[19] being an exception

Wikner,[19] who found the same values for men and women between fifty and seventy years but above the age of seventy a 19 mm

ressure
repre-
panies
ecause
ie per-
cepted

risks *Practically the only other available material* consists of hospital populations, a material with a high negative selection, and of the part of the lower middle class and poorer class, which visits

This latter
nnot be
ompen-
ut both
nalyzed

life insurance material and Wikner[19] the in-patients in the free hospital (St Erik) for chronic diseases in Stockholm Exton, cited by Adams,[1] in a material of 5727 blood-pressure determinations from both rejected and accepted risks, found the incidence of elevated pressures (above 150 systolic and 100 diastolic) higher among women than among men in the ages above thirty years Saller[17] analyzed a material of 2468 men and 1743 women from the out-patient service of the University Clinic in Kiel From the age of twenty-one to thirty-five years, the systolic pressure was essentially the same for men and women, from the age of thirty-nine years on Saller found
age
diastol
higher
the diastol
age, the w
the men
strictly no
Saller from his material excluded all patients on whom the diagnosis was made of any disease known to be associated with either elevated or lowered blood-pressure Gelman[10] analyzed a group of presumably healthy working people, 2641 men and 1120 women, practically all under fifty years of age Below the age of thirty years there were more men than women with systolic pressures above 141 mm, between the ages of thirty and thirty-nine years 6 per cent of the men and 11 per cent of the women exhibited pressure above this figure, between forty and forty-nine years, the corresponding figures were 15 per cent of the men and 19 per cent of the women

Gager[9] analyzed the systolic pressures in 1000 men and 1000 women consecutively examined in the Cornell Clinic Under thirty

decidedly more women than men were found to carry pressures of 150 mm or more From

sity Hospital financially all belong to the lower class or to the lower

middle class This is checked by a special dispensary agency The patients come both from the city and from the rural districts and consist of laborers, farmers, housewives and working women Many have no medical complaint, but are examined as a routine procedure sometimes as a preliminary to tonsillectomy, sometimes for hospital employment A small percentage only come because of symptoms suggesting hypertension All patients admitted to the medical house service have been included in this study Excluded from the material were clear-cut cases of glomerulonephritis and aortic insufficiency It has been interesting to notice the infrequency with which the diagnosis of true nephritis has been made

Technique —The blood-pressure in all instances was determined with mercury manometers and by the auscultatory method The diastolic pressure has been considered as the beginning of the fourth phase that is, the point at which there is a change from a sharp to [illegible] by the complete [illegible] ere taken in the [illegible] thirty minutes to [illegible] essure was taken after the history had been solicited and near the end of the physical examination In this way the factor of exertion was eliminated and the element of excitement reduced

[illegible]

each of these groups has been compared as to sex and age distribution The age distribution has been analyzed by decades with the exception of the fifteen to nineteen years of age groups The age of the patient has been considered as that given, and not according to the nearest birthday although in many cases the patient will give his age at the next birthday when this is a month or two hence only

For the analysis standard statistical methods have been used *

* The following explanations and definitions might prove desirable

(a) The means are arithmetic averages based on 5 mm groupings of blood pressure records

(b) The standard deviations of the distribution are the root mean square deviations [illegible] by the square [illegible] iation of the [illegible] e distribution [illegible] of the squares taken [illegible] error is three or more

(h) A measure of difference is given by Pearson s χ^2 test (Pearson Karl on the test of Goodness of Fit Biometrica 14 186 192? 1923)

(i) P gives the probability of a given χ^2 occurring in a normal variation of one sample

Figs 84 and 85 show for the men and for the women separately the frequency distribution of systolic blood pressure in percentage of their respective age groups The charts have been constructed

ments the manometer scale is marked off in 2 mm intervals Thus

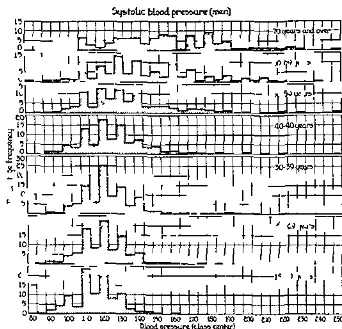


FIG 84 —Percentage frequency distribution of systolic blood pressure by 5-mm groups for men

there should be the same chances for readings on both sides of a 5 as around a 10 Actually this does not occur as shown by the charts The charts further show a practically symmetrical distri-

seventh groups

Table 37 shows the mean values standard deviations and coefficients of variability of the systolic pressure for the entire material,

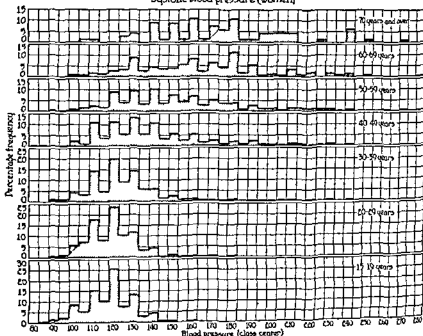


Fig 85 —Percentage frequency distribution of systolic blood pressure by 5-mm groups for women

TABLE 37 —SYSTOLIC BLOOD PRESSURE BY DECADES IN THE TOTAL MATERIAL

Men

Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation (σ)	Probable error	Coeff of variability
15–19	135	115 67	± 0 74	12 81	± 0 52	11 07
20–29	477	120 24	± 0 42	13 63	± 0 30	11 34
30–39	495	122 95	± 0 40	13 28	± 0 28	10 80
40–49	437	127 26	± 0 68	21 05	± 0 48	16 54
50–59	365	137 30	± 1 02	29 06	± 0 72	21 16
60–69	247	146 90	± 1 25	29 15	± 0 88	19 84
70 and over	126	158 10	± 1 79	23 86	± 1 27	18 89

Women

Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation (σ)	Probable error	Coeff of variability
15–19	285	117 93	± 0 47	11 81	± 0 33	10 01
20–29	731	119 55	± 0 55	12 94	± 0 23	10 82
30–39	786	125 83	± 0 48	19 79	± 0 34	15 73
40–49	636	139 43	± 0 75	27 92	± 0 53	20 02
50–59	513	152 92	± 0 96	32 04	± 0 68	20 95
60–69	241	163 92	± 1 43	32 97	± 1 01	20 11
70 and over	56	174 09	± 2 83	34 06	± 2 00	19 56

arranged according to sex and according to age, the latter expressed in decades (except for the age group fifteen to nineteen years) Both for men and for women there is a steady rise of the mean pressure from one age group to the other From the age of fifteen to thirty-nine years the rise is slight In the fifth decade (forty to forty-nine years) there is for the women a sudden rise of 14 mm, being just twice the rise in the preceding decade This rise brings the women 12 mm above the men, a difference which is not only maintained, but slightly increased during the following decades A sudden rise corresponding to the one just described occurs, to be
n in the women
the women has
pressure of the

This in a way is the main finding brought out in the present study, and the following discussion serves further to elucidate this point Attention shall be called to the fact that as this sudden break in the blood-pressure curve takes place, in the fifth decade for the women and in the sixth for the men, it is not only the mathematical mean that changes, but also the standard deviation and particularly the coefficient of variability, the latter becoming twice what

Table 37 and in Fig 86 that in the age group thirty to thirty nine years the mean pressure for the women is already slightly higher than the corresponding figure for the men, 2 88 mm to be exact

the commonly accepted requirement, that the ratio between the difference of the means and the probable error of the difference shall not be less than 3, it becomes evident from Table 38 (1) that the larger differences previously discussed possess a high degree of significance (the ratios for the age groups forty to forty-nine years and fifty to fifty nine years being 12 05 and 11 24, respectively), and (2) that even the small elevation of the mean pressure for the women between thirty and thirty-nine years above the corresponding mean for the men is of mathematical significance (the ratio being 4 64)

In order better to understand the meaning and significance of the changes in the mean pressures in men and women, a brief discussion seems useful before the presentation of any further tables It shall be remembered that the material under analysis consists of a practically unselected out-patient population, derived from

both city and rural districts—only instances of aortic insufficiency and definite chronic glomerulonephritis having been eliminated One might conceive of three different phenomena as the possible cause of the gradual elevation of the mean pressures There is first, the possibility that the pressure rises slightly in the population as a whole, further it might be that the elevations of the means are caused by a certain number of definite hypertensions mixed in

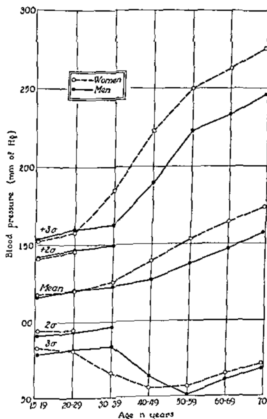


Fig 86 —Means and standard deviations of systolic blood pressure of men and women in different ages

with a large group of normal people possessing pressures the same as in the groups below thirty years for the women or below forty years for the men Finally and this alternative presents itself ... ences between ... ension ... ig the men There might also exist a combination of two or ... these possibilities Light is thrown upon these questions by Table 39

TABLE 38.—SEX DIFFERENCES BY DECADES FOR BLOOD-PRESSURE IN TOTAL AND ELEVATED SAMPLE

Systolic Blood pressure

Age group years	Total sample			Elevated sample		
	Diff (mm) women men	P E d ff (mm)	D ff / P E diff	Diff (mm) women men	P E d ff (mm)	Diff / P E d ff
15 19	2 [illegible]6	0 88	2 57			
20–29	−0 60	0 69	1 00			
30–39	2 88	0 62	4 64	1 43	3 04	0 47
40–49	12 17	1 01	12 05	5 84	2 40	2 43
50–59	15 62	1 39	11 24	0 46	2 21	0 21
60–69	17 02	1 89	9 00	5 44	2 40	2 26
70 and over	15 99	3 34	4 79	9 25	3 17	2 91

Diastolic Blood-pressure

Age group years	Total sample			Elevated sample		
	Diff (mm) women men	P E diff (mm)	D ff / P E diff	Diff (mm) women-men	P E diff (mm)	Diff / P E diff
15–19	1 51	0 71	2 12			
20–29	−0 14	0 41	0 34			
30–39	0 26	0 44	0 59	2 71	2 55	0 87
40–49	4 01	0 58	6 91	2 90	2 03	1 42
50–59	4 40	0 74	5 94	0 45	1 50	0 30
60–69	4 99	1 06	4 71	0 72	1 65	0 44
70 and over	6 99	1 88	3 72	3 16	2 18	1 45

TABLE 39.—THE FREQUENCY OF SYSTOLIC BLOOD-PRESSURES ABOVE CERTAIN LEVELS IN THE DIFFERENT AGE GROUPS OF MEN AND WOMEN IN PERCENTAGE

Mm Hg	15–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70 years and over
Men							
150	1 48	2 94	4 84	12 38	26 31	42 88	61 90
160	0 74	1 26	2 61	7 12	18 63	34 38	46 82
180		0 21	1 40	2 99	8 50	15 36	28 56
Women							
150	1 05	3 01	10 33	40 89	50 50	66 82	78 78
160	0 35	1 10	5 87	32 24	38 03	56 45	68 17
180		0 41	3 07	21 55	19 22	34 04	42 40

This table shows that a noticeable number of cases of moderate elevation of blood pressure start to appear ten years earlier among the women than among the men (thirty to thirty nine year group women *vs* forty to forty nine year group men) This incidence of rather moderate elevation of systolic pressure increases rapidly among the women but more slowly among the men as seen in the table where figures of the same order of magnitude for men and women have been underlined Thus in regard to frequency of elevated systolic pressure the women in the age forty to forty nine year group are as badly off as the men twenty years later This is well brought out for pressures above 150 and above 160 mm Hg

A test of significance was made for the comparative incidence in men and women of the occurrence of a systolic pressure of 150 mm or over Pearson s χ^2 test (see *h* in footnote page 372) gives a measure of difference which is interpreted directly on a probability scale P (*i* in same footnote) measures the chance that a difference would occur in a normal variation Thus in Table 40 P = 0.8 corresponding to a $\chi^2 = 0.1432$ in the fifteen to nineteen years of age group for systolic pressure means that there are 8 chances in 10 that the men and women in the given group are not differentiated with respect to the incidence of blood pressure over 150 mm or there are 2 chances in 10 that they are so differentiated Table 40

TABLE 40 —COMPARATIVE INCIDENCE FOR MEN AND WOMEN OF SYSTOLIC BLOOD-PRESSURE OF 150 MM AND OVER AND DIASTOLIC BLOOD-PRESSURE OF 100 MM AND OVER

Age group years	Systolic blood pressure		Diastolic blood-pressure	
	χ^2	P	χ	P
15–19	0.143	0.800	0.583	0.800
20–29	0.299	0.800	0.003	0.800
30–39	10.375	0.016	2.[illegible]54	0.527
40–49	39.160	0.000	19.103	0.000
50–59	61.952	0.000	11.020	0.01[illegible]
60–69	25.977	0.000	3.97[illegible]	0.[illegible]65
70 and over	6.139	0.106	3.740	0.295

Whether the elevated systolic pressures among women are of greater height than among men is tested in Table 41 which includes all individuals with a pressure of 150 mm Hg or more If the means for the women are compared with the means for the men age group for age group and the differences tested as to significance in the usual way no significant difference between these two sets of figures is found to exist

TABLE 41 —MEAN SYSTOLIC BLOOD-PRESSURES FOR THE GROUPS OF MEN AND WOMEN, WHOSE PRESSURE IS 150 MM HG OR MORE

Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation (σ)	Probable error	Coeff of variability
Men						
30–39	22	169 36	± 2 45	17 05	± 1 73	10 07
40–49	52	169 36	± 2 08	22 20	± 1 47	13 11
50–59	91	177 43	± 1 90	26 87	± 1 34	15 14
60–69	103	174 89	± 1 37	20 60	± 0 97	11 78
70 and over	77	176 64	± 1 63	21 18	± 1 15	11 99
Women						
30–39	73	170 79	± 1 80	22 76	± 1 27	13 32
40–49	177	175 21	± 1 21	23 84	± 0 85	13 60
50–59	247	177 89	± 1 21	26 23	± 0 79	14 74
60–69	156	180 33	± 1 98	36 63	± 1 40	20 31
70 and over	52	185 88	± 2 72	29 13	± 1 93	15 67

TABLE 42 —DIASTOLIC BLOOD PRESSURE BY DECADES IN THE TOTAL MATERIAL

Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation (σ)	Probable error	Coeff of variability
Men						
15–19	135	73 37	± 0 59	10 20	± 0 42	13 90
20–29	474	77 38	± 0 33	10 81	± 0 24	13 97
30–39	495	79 90	± 0 34	11 10	± 0 24	13 89
40–49	437	81 62	± 0 44	13 48	± 0 31	16 52
50–59	365	85 20	± 0 56	15 93	± 0 40	18 70
60–69	247	87 83	± 0 74	17 19	± 0 52	19 57
70 and over	126	87 86	± 1 00	16 67	± 0 71	18 97
Women						
15–19	285	74 88	± 0 39	9 71	± 0 27	12 97
20–29	731	77 24	± 0 25	9 94	± 0 18	12 87
30–39	786	80 16	± 0 28	11 72	± 0 20	14 62
40–49	636	85 63	± 0 38	14 11	± 0 27	16 48
50–59	513	89 60	± 0 48	16 21	± 0 34	18 09
60–69	241	92 82	± 0 76	17 54	± 0 54	18 90
70 and over	66	94 85	± 1 60	19 23	± 1 13	20 27

the systolic There is, however, a steady rise in the mean pressure

by decades for both men and women Until the fifth decade (forty to forty nine years) the pressures are about the same in men and women At this point the women show an abrupt rise their mean pressure exceeding that of the men by 4 mm In the sixth decade the men show similar elevation of the mean diastolic pres

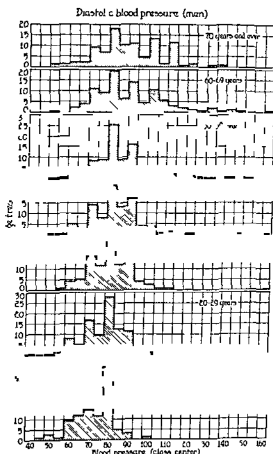


FIG 87 —Percentage frequency distribution of diastolic blood pressure by 5-mm groups for men

sure There is a continued rise for the women so that the mean diastolic pressure for the women is higher than for the men in all decades of life over forty years The standard deviations and the coefficients of variability rise much the same as for systolic pressure The differences between the means for women and men are statistically significant in all age groups over forty years as shown in Table 38 though of lesser magnitude than for the systolic pressures

Prior to forty years of age about the same percentage of men [illegible] 90 and 100 mm as [illegible]

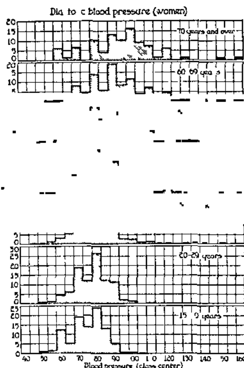


Fig 88 —Percentage frequency distribution of diastolic blood pressure by 5-mm groups for women

stolic pressures exceeding 100 mm among men and women For the age groups higher than forty years the P s indicate a definite probability that the women have a significantly higher percentage of diastolic pressures exceeding 100 mm Hg

For individuals with diastolic pressures in excess of 100 mm the *mean pressures are about the same for corresponding age groups* of men and women (Table 44) There are no significant differences (Table 38)

TABLE 43 —THE FREQUENCY OF DIASTOLIC BLOOD-PRESSURES ABOVE CERTAIN LEVELS IN THE DIFFERENT AGE GROUPS OF MEN AND WOMEN IN PERCENTAGE

Mm Hg	15–19 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70 years and over
Men							
90	5 18	16 44	24 85	29 99	38 34	46 15	46 83
100	1 48	2 10	4 85	8 48	16 70	27 12	30 96
Women							
90	7 36	15 60	24 03	40 26	50 70	62 66	69 73
100	1 05	1 92	6 09	16 83	24 17	34 45	45 48

TABLE 44 MEAN DIASTOLIC BLOOD-PRESSURES FOR THE GROUPS OF MEN AND WOMEN WHOSE PRESSURE IS 150 MM HG OR MORE

Age group years	No of cases	Mean pressure (mm)	Probable error	Standard deviation (σ)	Probable error	Coeff of variability
Men						
30–39	18	107 72	± [illegible] 19	13 77	± 1 55	12 78
40–49	29	112 90	± 1 90	15 21	± 1 35	13 46
50–59	55	113 35	± 1 26	13 8[illegible]	± 0 89	12 19
60–69	58	111 79	± 1 19	13 43	± 0 84	12 02
70 and over	36	108 19	± 1 10	9 76	± 1 10	9 02
Women						
30–39	43	109 9[illegible]	± 1 30	1[illegible] 65	± 0 9[illegible]	11 50
40–49	98	110 00	± 0 71	10 49	± 0 51	9 54
50–59	116	112 90	± 0 81	12 95	± 0 57	11 47
60–69	76	112 51	± 1 15	14 90	± 0 8[illegible]	13 [illegible]4
70 and over	28	111 36	± 1 88	14 76	± 1 33	13 [illegible]6

Discussion The preceding analysis has revealed that women exhibit an elevated systolic blood pressure more frequently than men that this difference is noticeable already in the age group thirty to thirty nine years and becomes more marked in the following decade during which as many instances of elevated blood pressure are to be found among the women as one finds among the men who are twenty years older Among the individuals who show a systolic pressure of 150 mm Hg or thereabove men and women do not seem to differ in any significant way as to the degree of the elevation of the pressure

We must remember that this is a statistical study of blood pressure and not a clinical study of hypertension consequently, no records of the presence of concomitant signs of hypertension (en

largement of the heart retinal arteriosclerosis etc) among the individuals exhibiting a pressure of 150 mm or more have been worked up for inclusion in this chapter Neither has the constancy of the elevation of the blood pressure been studied in detail Caution must therefore be taken in discussing to what extent the difference between men and women so clearly brought out by the

and others If a greater blood pressure lability among women is the explanation for the differences brought out in this study then it becomes necessary to introduce a new assumption namely the development of such an increased lability among women above the age of twenty nine years since no trace of such a sex difference can be noticed in the two age groups below thirty years where not only the mean pressures but also the standard deviations are the same for both sexes The author does indeed hesitate to introduce such a new concept

There exist certain indications that chronic hypertension in its course and outcome behaves as a milder disease among women than among men In the out patient service of the University Hospital where there is little difference between the number of men and women above the age of fifty years there are a number of women with elevated pressures but very few men who have been followed over a period of several years Blackford Bowers and Baker[6] in a follow up study of patients with systolic pressures of 175 mm Hg or more found 65 per cent to be women while their general clientele did not show any such sex preponderance Their patients were followed from five and a half to eleven years and showed during this time a mortality of 70 per cent for men and 39 per cent for the women The average length of life after the diagnosis had been made was longer for the women than for the men Riseman[15] likewise comments upon the relatively benign nature of hypertension in women

Applying these facts to our problem a more benign course of

for the most surprising result of our analysis the early appearance of elevated pressures in the women between thirty and thirty nine years neither is it applicable for the great difference in the age between forty and forty nine years where out of the men there were only 12 per cent with pressure above 150 mm as *versus* 41 per

cent among the women There exists no such mortality from hyper tension or its sequels among men of this age to produce this sex difference among the surviving

It is a matter of importance how to correlate with the findings of this study the results obtained from autopsies We are fortunate to be able to compare with our blood pressure studies the detailed report by Bell and Clawson[5] based upon a large autopsy material from the same community as our patients. Bell and Clawson used hypertrophy of the heart (in the absence of valvular lesions or chronic glomerulonephritis) as the chief diagnostic sign (for details see original article[5]) Thus it is clear that only such elevated blood pressures as were sustained over sufficiently long time and at sufficiently high level to produce a marked hypertrophy of the heart can have become included in the study of Bell and Clawson In their total material of 4578 autopsies on individuals between twenty one and eighty years of age, Bell and Clawson found 420 cases of chronic hypertension Among these they found the corrected ratio of men to women as 1 4 to 1 For the whole hyper
[illegible]

In the group of coronary sclerosis the ratio of men to women was 2 7 to 1 Eliminating the cases of coronary sclerosis the ratio for the remainder becomes 1 1 to 1 In the study of Bell and Clawson about 15 per cent of the individuals who died at an age above fifty years were afflicted with hypertension

The author s statistical results are based upon the behavior of the systolic pressure to a greater extent than upon the diastolic though the diastolic reveals the same sex difference but less pro nounced Thus his material besides the elevation of systolic pressure also reveals a corresponding general increase in pulse
[illegible] Saller[17] and

small autopsy material the hypertrophy of the heart was [illegible] pronounced This the author believes indicates the line along which the discrepancy between his statistical results and results based upon autopsy material is to be interpreted

On the basis of the previous discussion it seems justifiable to state that elevated blood pressures are found both earlier in life and with greater frequency among women than among men From the type of the curves and character of the tables presented there seems to be no support for any correlation of the facts in regard to the women with the phenomenon of menopause It further seems obvious that there exists a rather large number of individuals with pressures temporarily or permanently in excess of average levels

It is with purpose that no word has been said about what constitutes a normal blood pressure—in order not to detract attention from the essential problem of this study It might be of interest to return to Fig 86 where on each side of the means lines have been drawn through points representing the distances from the means of three times the standard deviations ($\pm 3\sigma$) According to established biometrical rules this distance three times the standard deviation represents the limit outside of which any given determination must fall in order to be considered as differing significantly from the mean It should be added that in order to make such a rule hold it is essential that the material for which the mean has been calculated shows a practically symmetrical distribution such as the author s material does for the two lower age groups of Figs 84 and 85 It should further be added that if this condition is fulfilled about 95 per cent or more of the single determinations from which the mean has been calculated will fall within plus and minus twice the standard deviation

For the author s particular case only the material from the age of fifteen to thirty nine years for the men and from fifteen to twenty-nine years for the women lends itself to a discussion of normal systolic blood pressure On this point the reader is asked again to inspect Table 39 where the figures to the left of the ⌐ in the same line as 150 (mm Hg) well illustrate what has just been stated Returning to Fig 86 lines through the points representing plus and minus twice the standard deviation have been laid in for these age groups only ($\pm 2\sigma$)

Practically all discussions of normal systolic blood pressure in man have been carried on with the hope of being able to draw a definite line of distinction between a normal pressure and an early pathological hypertension Compared with the number of such attempts the discussions devoted to the differentiation between

once and for all between a normal pressure and an early hypertension is a futile one As will be seen by comparing the figures in Table 39 for the age group twenty to twenty nine years for instance with the blood pressure values represented by $+2\sigma$ and $+3\sigma$ in Fig 86 the cases with blood pressures between the values of $+2$ and $+3$ times the standard deviation or between 147 and 160 mm Hg are insignificant in number and no one would dare to state on the basis of a single blood pressure reading whether they represent an early hypertension or not

When cases of the same pressures start to accumulate in number as in the group of women between forty to forty-nine years for instance, they become significant in a different way now they form to a great extent the lower pressures among a group of hypertensions as indicated in an indirect way by the enormous increase of the standard deviation of the mean for this group and we are statistically at a loss in determining the upper limit of a normal pressure for this age We are at a loss because we possess no rule for a selection of our normal material, the needed dividing line being at the same time what we search for, and what we need to apply in order to find what we search

For practical purposes the way out of this dilemma is the one followed by the actuaries of the life insurance companies the determination of the pressure above which the death rate rises above the rate known to hold for the same age groups without elevation of blood pressure

The author wishes to use this opportunity to express to Miss Marie M Ness his appreciation of her invaluable aid in the statistical analysis

REFERENCES

1 ADAMS S F 1929 A study of the blood pressure of patients with diabetes mellitus Am J Med Sci, 177 195–201

2 ALVAREZ W C 1920 Blood pressure in university freshmen and office patients Arch Int Med 26 381–404

5 BELL, E T AND CLAWSON B J 1928 ... sion Arch Path 5 929–1002

... 1930 Follow up

J Med Sci 173

8 FLEISCH A 1927 Der normale Blutdruck Handb d norm u pathol Physiol 7 1267–1302

9 GAGER L 1928 The incidence and management of hypertension J Am Med Assn 90 82–86

10 GELMAN J 1927 Hypertoniestudien Alters und Berufsverschie- ... Med 106 310–319

mal and

is varia re Am

on Am

Assn 73

350–352

16 RISEMAN J E F AND WEISS S 1929 The age and sex incidence of arterial hypertension Am Heart J 5 172–190

17 SALLER K 1928 Ueber die Altersveranderungen des Blutdruckes ... 58 683 709

ure of healthy men and women

llskapets Handlingar 42 1489

CHAPTER XXIII

ELEVATED BLOOD PRESSURE

By FRANZ VOLHARD M D

Motto In the high pressure I see the cardinal problem of the entire renal pathology

Introduction —The problem of hypertension is nearly a hundred years old Today it occupies the center of interest, there are reasons to believe that its solution is not far away The problem arose when Bright observed hypertrophy of the left ventricle of the heart among his cases of kidney disease The knowledge of this puzzling relationship possibly is older, does not the Bible speak about "searching the heart and the reins ?" When in the middle of the last century the tension of the pulse became the subject for intensive clinical studies advances were necessarily made in regard to the occurrence, origin and significance of the hypertrophy of the heart in kidney diseases, from this hypertrophy an idiopathic heart hypertrophy was still held as a separate entity When it finally became possible clinically to measure the pressure in the [illegible]

[illegible]

[illegible]

The question was no longer *why* does the heart hypertrophy in many instances of kidney disease, but *how* does the hypertension arise both in kidney diseases and in the old 'idiopathic' hypertrophy and how explain a hypertension in patients not yet displaying any enlargement of the heart?

It is a commonplace statement that two factors are involved in the rise of blood-pressure, peripheral resistance and heart force or rather time volume Thus the pressure will rise (1) as the result of an increase of volume flow, the peripheral resistance remaining constant and (2) by an increase in peripheral resistance, the volume flow remaining constant Under the first alternative with a sustained increase of the output per beat we expect an "excentric' length hypertrophy of the left ventricle, as in aortic insufficiency, in the second alternative with an increased peripheral resistance we expect a concentric hypertrophy chiefly in the thickness of the ventricular wall as in aortic stenosis Since in pathological hypertension concentric hypertrophy is the rule, at least in well com-

pensated early stages it might *a priori* be assumed that the rise in pressure is caused by increased peripheral resistance In fact an increase in blood volume or in minute volume has not been demonstrated at least not with any degree of regularity In regard to increased resistance the possibility exists that the viscosity of the blood is increased with the result that the flow through the finer vessels takes place with increased friction This assumption should be abandoned There are cases of hypertension with increased viscosity of the blood but more frequent are the cases of polycythemia and increased viscosity which present normal pressure

The increase in resistance has been pictured as organic and attributed to alterations in the arterioles particularly in so called arteriolosclerosis but also in acute nephritis However in acute nephritis no changes can be demonstrated in the arterioles and in arteriolosclerosis *the characteristic lesions are present only in the kidneys*

functional rather than organic

The French are inclined to find the causative factor in a hyperadrenalinemia while in Germany one is accustomed to consider a central or reflex stimulation of the vasomotor center This center regulates the blood pressure to a considerable extent through the bloodvessel bed controlled by the splanchnic nerves no great change of pressure takes place without the participation of the tonus and the filling of the vessels within the large region of the intestines But splanchnic stimulation causes an increased outpouring of the hormone of the suprarenal glands and it seems questionable whether under physiological conditions one can produce an increase of blood pressure of any considerable duration without the participation of adrenaline It has long been known [illegible] nchnic ind on cluded that every rise of blood pressure brought about by the agency of the nervous system involves the cooperation of the chemical mechanism represented by the suprarenal glands This *conception has for many years been the subject of most vigorous* attacks and deadlock seemed sometimes threatening As usual the solution came through new and improved experimental methods which methods also gave results beyond the point under dispute Generally speaking the problem was the clear-cut demonstration of the relative role of the chemical and the nervous factors in the control of circulation

Improved methods for crossed circulation experiments seemed to promise results *Tournade* Chabrol and Marchand[23] made an

anastomosis between the suprarenal vein of one dog (B) and the jugular vein of another (A) Dog A had both suprarenals previously removed and dog B had the non anastomosed suprarenal removed A nervous stimulation of the dog with the adrenal (B) thus will result in a chemical response in the dog (A) with both adrenals removed, while the dog with the adrenal (B) is capable of nervous response only

Anrep[2] arranged for crossed circulation experiments by the use of one dog and a Starling's heart-lung preparation, in this way obtaining complete control over blood flow and blood pressure in the "donor, the heart-lung preparation, thus avoiding one source of error in earlier methods This method still left the systemic circulation of the recipient dog uncontrolled This disadvantage Anrep was able to overcome by a new technique which might be called an *innervated* heart-lung preparation which allows an independent control over the circulation in the brain and in the heart Finally J I Heymans developed a method in which the circulation of the head of the recipient dog is taken care of by the donor, the recipient's head being completely separated from its own body except for the nerves within the sheaths of the two vagi Though conflicts exist between the results obtained by different investigators, they are surprisingly few and it seems possible to obtain a view, at least grossly coherent of the mechanisms which regulate blood-pressure and circulation

According to Tournade and Chabrol[23] on splanchnic stimulation of the donor (B) there occur in the same animal an immediate rise

stimulation of the donor (B) after a delay of ten to thirty seconds is followed by a marked rise in blood pressure lasting three or four

conditions and plays a rôle in the maintenance of the vascular tone

When the blood pressure of the donor was reduced by bleeding adrenalin secretion resulted and the pressure in the recipient rose The reverse occurred when the blood pressure in the donor was raised by intravenous blood injection by stimulation of the splanchnic on the suprarenalectomized side or by injection of adrenalin the adrenalin output from the donor diminished and the blood pressure fell in the recipient Anrep and Daly[3] used the heart lung preparation to perfuse the lower half of a second animal (recipient) When the splanchnic of the recipient was stimulated or when anemia of the brain was produced in the recipient adrenalin was discharged as indicated by acceleration of the heart in the heart lung preparation and by the failure of this acceleration to occur if the suprarenals of the recipient had been previously removed or denervated

Turning from the hormonal to the nervous regulatory mechanism the consideration of both central and reflex phenomena call for our attention Such consideration by necessity deals with a multitude of combinations which though generally known are not easily kept clearly in mind The informed reader therefore will have to overlook the repetition of facts which seem to him commonplace

Of centers the vasomotor and the cardio inhibitory ones are of greatest importance These names the reader will notice are functional only morphologically the former repre ents part of the sympathetic centers scattered in the medulla and might possibly be located near the nucleus of the facial nerve the latter is a part of the vagus center Though Bayliss is correct in his statement that the substitution of the name vasomotor for the accurate vasoconstrictor may cause confusion the name vasomotor is commonly applied These centers have been shown normally to respond to two different types of stimulation reflex stimulation from afferent impulses and central stimulation from variations in blood pressure within the centers themselves Pathological response follows acute anemia asphyxia and altered composition of the blood The receptors of the different reflex arcs normally respond to variations in pressure only The efferent arcs from the vasomotor and cardio inhibitory centers are the sympathetic and the vagi respectively Of afferent reflex arcs we know of two pairs the depressor nerves going in the vagi and the connections between the carotid sinus and the medulla said by Hering[1] to follow the glossopharyngei and named the sinus nerves Hering has named the depressors and sinus nerves *Blut druck ugler* The receptors of the depressors are spread over a wide area Using the slowing of the heart as response and increased pressure as stimulation Daly and Verney[8 9] found receptors present in the ventricular wall of the heart and in the aorta as far onward as the upper part of the descending aorta The receptors in the carotid sinuses are concentrated over a smaller area and seem to

have a maximum concentration right in the slightly sacculated carotid sinus

Anrep and Starling[9] studied the effects of *central* stimulation of the vasomotor and cardio-inhibitory centers Acting synergetically these centers control the blood-pressure in the following way Inhibition of the vasomotor center causes vasodilatation, stimulation of the cardio-inhibitory center causes slowing of the pulse, the latter occurring when the vagi are intact and both reactions together lowering the pressure A mechanical rise of the blood pressure in the brain inhibits the vasomotor and stimulates the cardio-inhibitory center Or in terms of the actual experiments When the blood-pressure in the brain was reduced, an immediate vasoconstriction in the animal took place, and *vice versa*, when the pressure in the brain increased an abrupt vasodilatation in the rest of the body occurred Or again in general terms *Changes in the blood-pressure in the vasomotor center produce the reverse changes in the blood-pressure in the rest of the body* The effect is almost immediate, the latent period being measured in fractions of a second The changes occur whether the vagi be cut or intact, they are based on a *central* mechanism and are vasomotor in origin The rise or fall in the systemic blood-pressure produced by the reverse in the brain, is not of a transitory nature, but lasts until the pressure in the brain changes

In regard to the heart-rate (Anrep and Starling[9] Anrep and Segall,[4] Nash[17]), when the blood pressure in the brain was reduced an immediate acceleration of the heart followed, when the cerebral blood-pressure was raised the heart slowed down, these responses disappear after section of both vagi

Asphyxia produced by cerebral anemia causes the blood pressure to rise and slows the pulse Thus a stimulation is produced of both the vasomotor and cardio-inhibitory center at the same time, instead of the synergetic action of the two centers in response to a "physiological stimulus we observe an antagonistic response following this "pathological stimulation

In regard to the *reflex* regulation of the blood-pressure, a rise of pressure in the aorta has exactly the same effect as a rise of pressure in the centers themselves producing an inhibition in the vasomotor and a stimulation in the cardio-inhibitory center resulting in a general vasodilation and fall in blood-pressure, together with a slowing of the pulse These depressor effects are abolished on section of both vagi

Hering s carotid sinus reflex represents a second reflex regulation of the blood-pressure identical as far as one can see, with the depressor mechanism just described in every respect, except the localization of its receptors in the region of the carotid sinus, the reflex usually is stronger on the right side than on the left (Hering,[11] Heymans[12])

The main discrepancy which exists at present between the different investigators is that what Starling Anrep etc have described as central regulation Hering and Heymans interpret as Hering s *reflex regulation through* pressure changes in the carotid sinus

These facts then represent the high spots in our knowledge of the normal regulation of blood pressure The author s sketch has been left incomplete The reciprocal effect of the vagus and the sympathetic (the accelerator) on the heart rate he has not touched upon neither has he discussed the tone of the depressor and the sinus nerves the regulating effect of which becomes visible when it is abolished by *section of these nerves a procedure followed by a sus*tained and under certain circumstances a most considerable rise in blood pressure The possible existence of an independent pressor reflex and of independent vasodilators likewise purposely have been left untouched

This sketch impresses upon us certain general principles in normal

for elevation of pressure But the elevation might be overdone

predominantly as protective mechanisms against high pressure The normal peripheral mechanism for the lowering of pressure is indeed an efficient mechanism But still more is one impressed by the richly worked out reflex mechanism for setting this pressure reduction in action with pressure sensitive areas in the heart and aorta in the large arteries leading to the brain and in the brain itself A further safeguarding of the undisturbed function of areas sensitive to extracerebral pressure is accomplished by the provis on *of separate nerve paths*

Still in spite of this seemingly fool proof mechanism deleterious chronic hypertension exists

Against the background of the normal regulation of the blood pres ure we proceed with the *analysis of chronic hypertension* What is the relative importance of the two mechanisms the nervous

whole arterial bed

recognition of two di tinct forms of chronic hypertension Clinical observation led to such a recognition Certain instances of h gh pressure must be caused by a contraction of all vessels in others this seems not to be the case

In the first group the patients are pale in the second they are

ruddy The kidneys of the first group at autopsy are found to be pale in the second red The pale patients are sick tired and weak

constriction and the typical ischemic disease of the retina is apt

maximal narrowing of their arterial branches but not so in the red patients In instances of pale hypertension one recognizes at a distance that the patient is ill with kidney disease he presents the characteristic picture of a general arterial ischemia The red ones rather figure as general hyperemias

In the group of pale hypertension belong nephritic patients with tendency to develop retinitis angiospastica The group termed red hypertension includes what once used to be called idiopathic hyper trophy of the heart and what today is usually named permanent or

disease picture though it may not have become more frequent yet has become better known is one of the great puzzles of present day medicine

ical mechanism of pale hypertension are we dealing with an enrich ment of the blood with the suprarenal hormone? After amounts of difficult method cal forework the author s co worker Hulse, using arterial blood for his studies was able to answer this question in the negative Hulse s results speak against the doctrine of hyper-adrenalinemia and also against the assumption of a central or peripheral excitation of the vasomotor center or of the splanchnic as the cause of the general vasoconstriction in pale hypertension—because such an excitation should produce a hyperadrenalinemia *The assumption of a purely nervous origin of red hypertension* likewise becomes improbable Even if a short rise of pressure by purely nervous stimulation is possible through the effect of the splanchnic we are dealing with a neuro-hormonal mechanism and the hormonal component could not remain inactive in sustained hypertension

It is possible that instances occur in which paroxysmal or sustained hypertension is brought about by hyperadrenalinemia Such might be the case in patients with hypertension and tumors in the suprarenals observed by others and by ourselves It might also be the case in carbon monoxide poisoning and in transitory reflex

Normal physiology possesses no analogy to this pathological phenomenon It falls not within the borders of the known Each mechanism must be investigated and explained separately

THE CHEMICAL MECHANISM OF PALE HYPERTENSION

Continuing his experiments Hulse raised the question whether in hypertension substances are present in the circulation which sensitize the vessels to adrenalin Animal experiments showed that the same amount of adrenalin always produced the same blood pressure effect no sensitization resulting from repeated injections Neither did the addition of normal human serum to the adrenalin have any effect upon the height or shape of the blood pressure curve resulting from the adrenalin injection In contradistinction to these results the addition of nephritic serum distinctly augmented the effect of the adrenalin Serum from benign or red hypertension does not exercise the same sensitizing effect For the latter group we had from clinical considerations already assumed no vasoconstriction to be present This seemed to confirm our suspicion that an increase in peripheral resistance leading to hypertension might be produced in more than one way

In hypertension with general vasoconstriction as exemplified in chronic diffuse nephritis the periphery seems the point of attack and the constriction appears to be chemically conditioned An

patients with pale hypertension react to the smallest amounts o *adrenalin intravenously injected* with a rise of pressure whereas patients with red hypertension do not react to the same small doses

Another step in the characterization of the serum of pale hypertension was taken through the observations of Kato and Watanabe[6] that the serum from chronic but not from acute nephritides has a sensitizing effect upon peripheral sympathetic fibers and more so the higher the blood pressure in the patient who supplied the serum These workers tested the electrical excitability of the sympathetic observing the effect on the pupil Tashiro[5] found this sensitizing

effect upon the sympathetic in sera from patients afflicted with chronic diffuse nephritis with hypertension and in malignant hypertension but not in essential or benign hypertension or in chronic glomerulonephritis without elevation of the blood-pressure

In animal experiments Major[41] has demonstrated a prolonged elevation of the blood pressure following injection of guanidine In 15 instances of chronic nephritis Major concluded that guanidine was present in the blood in increased amounts (13 of these cases showed retention of nitrogen at the same time) and the same he found to be the case in 61 per cent of his hypertension patients He did not differentiate between simple and malignant hypertension

Concerning the chemical qualities of the sensitizing substance Hulse and Franke[41] have found it easily adsorbed by charcoal soluble in alcohol ether acetone and chloroform as well as water After precipitation with alcohol the protein free plasma filtrate upon acid hydrolysis shows a definite increase in amino nitrogen with Van Slyke s method while such an increase is not obtained with
[illegible]

negative phenol reaction Hulse and Franke[41] think of phosphatides and have especially suspected cholamine (amino-ethyl alcohol) Cholamine chlorhydrate after intravenous injection in curarized cats causes a long sustained marked rise of blood pressure

Dancer Brody and Miles[36] report on a pressor substance in whole blood from patients with hypertension Their results were not confirmed by Curtis Moncrieff and Wright[36] nor by Bodenstab[33] Continuing on the author s suggestion the search for pressor substances Bohn[31] found that an alcoholic extract of 30 cc blood from patients with pale hypertension produced in a cat a noticeable rise of pressure amounting to as much as 30 mm Hg and continuing for more than one half hour Alcoholic extracts from the blood of normal individuals and of patients with red hypertension caused the pressure to fall so did the blood from 3 patients with focal nephritis and 3 patients with chronic nephritis without hypertension At present blood has been examined from 70 normal individuals nearly 100 patients with red hypertension and approximately 100 with pale hypertension Results as described were obtained in nearly 90 per cent of the pale hypertension material This pressor effect occurred in animals even after section of the cervical cord indicating a peripheral action of the substance The attack seems to be on the vessel wall constriction having been observed of the surviving vessels of the rabbit s ear Perfusion experiments on intestinal loops resulted in both arterial and venous constriction Active extracts give a stronger blue color with the ninhydrin reagent than inactive ones pointing to a possibility of quantitative estimations

The author feels that these observations of biological responses offer strong support for the assumption of a chemical mechanism of pale hypertension, an assumption independently arrived at through clinical observation and based upon the paleness, the narrowing of the capillaries and the angiospastic retinitis As to the nature of the pressor substance or substances nothing can be said at present Of immediate interest is the question of their origin and whether they are identical in all cases of pale hypertension Possibly these substances originate from infections, particularly streptococcic infections including scarlet fever, or they might

that it occurs in kidney damage only Various kinds of damage will be drawn into our discussion

1 In a first group are included conditions in which the renal origin of the hypertension *cannot be doubted* (*a*) In every kind of anuria a rise in blood pressure is the rule (*b*) In urinary retention due to obstruction of the ureters by tumor, due to prostatic hypertrophy, narrowing of the urethra or to phimosis an elevated blood pressure is usually found After removal of the obstruction the cases the heart will hyper- condition which might be inary obstruction or as a nephrons, hypertension is found as a rule (*d*) In pyelonephritic and hydronephrotic granular kidney hypertension is not infrequently present (*e*) The same is the case in hypoplastic kidneys

That occasionally hypertension is absent in any one of the groups just mentioned and in every group to be mentioned presently, does not invalidate the general rule, it does not even prove with certainty that an elevated pressure was not present during some part of the course of the disease

treatment and also after surgical reduction of the mass of normal kidney tissue Correlating the clinical and experimental results of the biological test for pressor substances, positive findings have been obtained as follows in 2 instances of anuria, in 1 instance of

hypertension resulting from compression of the ureters by a car

responsible for the appearance of the pressor substances in the blood It might be recalled that Tigerstedt and Bergman[53] found pressor substances in extracts from normal kidneys

2 In a second *angiopathic* group are brought together some conditions in which the high pressure seems to be renally conditioned (*a*) Rare instances of primary endarteritis of the renal arteries and (*b*) the very rare instances of hypertension in granular kidney due to amyloid

Endarteritis of the renal arteries with secondary contraction occurs in syphilis and rarely in tuberculosis Whether the hypertension in these cases develops prior to the renal insufficiency is not known Here also belongs the endarteritis of the renal arteries which occurs as a part of the picture in periarteritis nodosa In this peculiar infectious disease hypertension develops only when the kidneys are involved Of this condition the writer has seen 1 patient resembling an acute nephritis with eclamptic uremia and a second one present

ditions unfavorable for its development (Albrecht and von Brochowski[30]) The author has had occasion to observe cases of this kind due to syphilis One patient died from renal insufficiency presenting the picture of eclamptic uremia retinitis angiospastica hyper

* He has since died of uremia. Autopsy showed the same severe amyloidosis as his brother had had

The author feel that these observations of biological responses offer strong support for the assumption of a chemical mechanism

at present Of immediate interest is the question of their origin and whether they are identical in all cases of pale hypertension Possibly these substances originate from infections particularly streptococcic infections including scarlet fever, or they might enter the blood from the intestinal tract Clinical and experimental facts point to the kidneys as the principal or only source

An inquiry into the clinical conditions correlated with pale hyper tension reveals that it occurs in kidney damage only Various kinds of damage will be drawn into our discussion

1 In a first group are included conditions in which the renal origin of the hypertension *cannot be doubted* (a) In every kind of anuria a rise in blood pressure is the rule (b) In urinary retention due to obstruction of the ureters by tumor due to prostatic hyper trophy narrowing of the urethra or to phimosis an elevated blood pressure is usually found After removal of the obstruction the pressure might fall but in long standing cases the heart will hyper trophy (c) In polycystic kidney a condition which might be looked upon as the highest seated urinary obstruction or as a multiple hydrone
found as a rule

one of the groups just mentioned and in every group to be mentioned presently does not invalidate the general rule it does not even prove with certainty that an elevated pressure was not present during some part of the course of the disease

The following experimental findings may be correlated with the clinical conditions mentioned In acute animal experiments hyper tension will occur after destruction of renal tissue after ligation of the renal artery on one side or after ligation of some of its branches al o after ligation of the ureter from one ki lney (Hartwich) Hyper
result in experi
ontracted kidney
he kidney lesions
produced by transitory ligation of the ureters or by roentgen ray treatment and also *after surgical reduction of the mass of normal* kidney tissue Correlating the clinical and experimental results of the biological test for pressor substances positive findings have been obtained as follows in 2 instances of anuria in 1 instance of

hypertension resulting from compression of the ureters by a carcinoma of the uterus in 1 patient with polycystic kidney in animal experiments in hypertension produced by unilateral ligation of the renal artery and of the ureter

(b) the very rare instances of hypertension in granular kidney due to amyloid

Endarteritis of the renal arteries with secondary contraction occurs in syphilis and rarely in tuberculosis Whether the hypertension in these cases develops prior to the renal insufficiency is not known Here also belongs the endarteritis of the renal arteries which occurs as a part of the picture in periarteritis nodosa In this peculiar infectious disease hypertension develops only when the kidneys are involved Of this condition the writer has seen 1 patient resembling an acute nephritis with eclamptic uremia and a second one presenting the typical picture of genuine contracted kidney with a blood-pressure of 200 mm Hg and hypertrophy of the heart

Almost as rare are the cases of uncomplicated amyloid contracted

due to syphilis One patient died from renal insufficiency present

was confirmed histologically A brother is alive* with pronounced

* He has since died of uremia Autopsy showed the same severe amyloidosis as his brother had had

The author feels that these observations of biological responses offer strong support for the assumption of a chemical mechanism of pale hypertension, *an assumption independently arrived at* through clinical observation and based upon the paleness the narrowing of
nature of
at present
and whether they are identical *in all cases of pale hypertension* Possibly these substances originate from infections, particularly *streptococcic infections*, including scarlet fever, or they might enter the blood from the intestinal tract Clinical and experimental facts point to the kidneys as the principal or only source
with pale hyper-
only Various

1 In a first group are included conditions in which the renal origin of the hypertension *cannot be doubted* (*a*) In every kind of anuria a rise in blood pressure is the rule (*b*) In urinary retention

pressure might fall but in long standing cases the heart will hyper trophy (*c*) In polycystic kidney a condition which might be looked upon as the highest seated urinary obstruction or as a multiple hydronephrosis of individual nephrons hypertension is found as a rule (*d*) In pyelonephritic and hydronephrotic granular kidney *hypertension is not infrequently present* (*e*) *The same* is the case in hypoplastic kidneys

That occasionally hypertension is absent in any one of the groups just mentioned and in every group to be mentioned presently does not invalidate the general rule it does not even prove with certainty that an elevated pressure was not present during some part of the course of the disease

The following *experimental findings may be correlated* with the clinical conditions mentioned In acute animal experiments hyper
all occur after destruction of renal tissue, *after ligation of*

tension and hypertrophy of the heart
ments leading to chronic kidney damage, as in the contracted kidney produced by chronic *cantharidin poisoning or in the* kidney lesions produced by transitory ligation of the ureters or by roentgen ray treatment and also after surgical reduction *of the mass of normal* kidney tissue Correlating the clinical and experimental results of the biological test for pressor substances positive findings *have been obtained* as follows in 2 instances of anuria, in 1 instance of

that the kidney was the source of these pressor substances, the theory of eclampsia would have to be rewritten Considering the frequency of compression of
possible Yet, so far, nobod
toxemia to be of renal origir
permanent hypertension resulting in rare cases, in which instead of recovery typical endarteritic changes of the renal vessels develop? Here the pressor factor of pregnancy is not operating any longer Must not here as in the chronic lead kidney the hypertension become renally conditioned? Do not these two types under these circumstances move back into the second or angiopathic group?

4 We have reached the pertinent problem of Bright's disease, the true hypertonic kidney diseases diffuse glomerulonephritis or secondary contracted kidney and malignant sclerosis or genuine contracted kidney In these diseases with tendency to retinitis angiospastica pale hypertension exists *viz*, a general vasoconstriction, chemically produced In these forms of pale hypertension pressor substances are found in the blood But serious disturbance of renal blood supply also exists If disturbed renal circulation leads to the appearance of pressor substances in the blood, the conclusion evidently offers itself that a renally conditioned elevation
c
a
r

The most difficult problem is presented by the pathogenesis of acute diffuse glomerulonephritis, a condition characterized by a greatly disturbed circulation through the glomeruli, how does this serious circulatory disturbance originate? The author has assumed that in the acute stage this disturbed circulation is caused by vasoconstriction rather than by anatomical alterations That besides the renal disturbance a general ischemia also exists is proved by the elevated blood-pressure and by the characteristic pale complexion of the patients, Hulse also demonstrated the presence of sensitizing and Bohn the presence of pressor substances in the blood Is the glomerular vasoconstriction but a part of the general ischemia or is the peripheral vasoconstriction secondary to the renal process? The power of tradition supports the latter view while in favor of the former speak the observations of an elevated blood-pressure sometimes preceding the onset of renal symptoms This interpretation would to a certain extent deprive the acute nephritis of its character of a primary kidney disease It would be included in the third group of angiospastic kidney diseases together with the lead and pregnancy kidneys Certain other observations speak against this

hypertension large liver and spleen and slight albuminuria A sister and mother died under exactly the same conditions, whereas the father, who is responsible for this uncanny tragedy and who years ago had a cranial tumor disappearing *after iodine enjoys the* best of health

Even in this angiopathic group the common factor operating in the elevation of the blood pressure might be sought in an inter-

sensitize the vessels to vasoconstricting and vasodilating substances (*Wolpe*[55]) *Lead hypertension might be looked upon as due to*

cases a typical contracted kidney results not to be distinguished *from a severe secondarily contracted kidney In such cases one* might be more inclined to correlate the hypertension with the

Rosenberg[47] Even taking into consideration the slow elimination of the lead after the poisoning has once taken place the question might be raised whether a disturbance of renal blood supply might not be the factor responsible for the *sustained hypertension even*tually leading to serious endarteritic lesions of the renal vessels

may be looked upon as a part of a general vasoconstriction *renally conditioned but responsible for the hypertension* As causative agents adrenalin like placentar substances or biogene amines have been suspected Alder's[3] findings of elevated values for the amino nitrogen in eclampsia could not be confirmed by Hulse and Strauss[45] *who suggest that Alder was deceived by the nin*hydrin reaction In the blood serum in eclampsia Hulse was able to demonstrate sensitizing substances Bohn[31] found pressor substances and increased ninhydrin reaction *If it could be proved*

[illegible]

Against the assumption of retention may be cited the fact that in pale hypertension a greater amount of them is found in the urine than in the case of normal individuals or of those with red hypertension. Again they might be products of disturbed metabolism [illegible]

such pressor substances appear in the blood. They are always present in retinitis albuminurica. The development of the retinitis and of renal insufficiency in hypertensive disease the author regards as effects of the pressor substances. The appearance of these substances in such a primary renal condition as polycystic kidney and after ligation of the artery or the ureter of one kidney supports the assumption that the kidney produces the conditions necessary for their appearance.

These substances, characteristic of pale hypertension, again are the cause of disturbed renal circulation with deterioration of kidney function—a vicious circle.

RED HYPERTENSION.

So far, red hypertension has been characterized in a negative way only, and it is easier to state what it is not than what it is. It is neither caused by general vasoconstriction nor is it of chemical nor of purely nervous origin. It is not, as the author earlier used to [illegible]

able to demonstrate typical lesions of the smaller arteries of the [illegible]

investigators, particularly Wallgren,[76] confirmed the frequent association of these changes with essential or red hypertension. Red hypertension, however occurs also without them. Impressed by the frequency of their coexistence, Jores[67] and also Wallgren suggested that the hypertension and the vessel changes were coördinated phenomena. Thus our problem becomes the demonstration of their common cause.

[illegible] even multiple [illegible] er in the pre- [illegible] ught be looked

viewpoint, namely the results of surgical interferences with the acute nephritic kidney, like decapsulation, splanchnic anesthesia and even diathermy or roentgen-ray treatment of the kidney region all intended to facilitate the *circulation* *Any one of these procedures* in certain instances produces an almost instantaneous diuresis, lowering of the blood pressure and sudden recovery Whatever the initial mechanism, the sustained vasoconstriction in the kidney must contribute to the maintenance and intensification of the general vasoconstriction

Do we have to consider a twofold origin of the pressor substances, a primary extrarenal, correlated with the infection, and a secondary due to the disturbance of renal function or circulation—a "renin" production? Or is, as we used to believe, a nervously conditioned vasoconstriction within the kidney the primary factor and the general *vasoconstriction the result of the disturbed renal circulation*, as we experimentally found hypertension follow after ligation of the renal artery or the ureter? In acute nephritis as well as in these experimental conditions Bohn found pressor substances in the blood within only a few days after the blood pressure had started to rise The appearance in acute nephritis of vasoactive substances with similar effect as in chronic renal hypertension the author looks upon as indicating that also in acute nephritis a disturbed renal circulation initiates the other symptoms The difficulty shall be admitted in reconciling this view with the observations of what we may call "prenephritis," the appearance of an elevation of the *blood-pressure prior to the onset of the urinary symptoms*, as one might observe under the influence of a recurrent streptococcus infection, during recovery from scarlet fever, from acute tonsillitis or after "colds"

Summary —In any form of chronic *hypertensive kidney disease* leading to deterioration of kidney function the chemical mechanism of pale hypertension plays a rôle A twofold relationship probably exists, the vasoconstricting substance or substances being the product of a diseased kidney and also a toxicant to the kidney, leading to renal insufficiency through lasting circulatory disturbances

It seems likely that in certain acute conditions of pale hyperten-

will further be found in conditions of chronic disturbance of the circulation, in certain but not all conditions of destruction of renal tissue and, as it appears, also when an insufficient amount of kidney mass is available

Different possibilities *evidently exist for the* assumed relationship between the kidney and the appearance of pressor substances in the

blood
metabol
earlier t
Against the assumption of retention may be cited the fact that in

and of renal insufficiency in hypertensive disease the author regards as effects of the pressor substances The appearance of these substances in such a primary renal condition as polycystic kidney and after ligation of the artery or the ureter of one kidney supports the assumption that the kidney produces the conditions necessary for their appearance

These substances characteristic of pale hypertension, again are the cause of disturbed renal circulation with deterioration of kidney function—a vicious circle

RED HYPERTENSION

So far red hypertension has been characterized in a negative way

able to demonstrate typical lesions of the smaller arteries of the kidneys in essential hypertension Hypertrophy of the elastica of the prearterioles and hyalinization of the arterioles changes looked upon as belonging to arteriosclerosis were present Subsequent investigators particularly Wallgren [76] confirmed the frequent association of these changes with essential or red hypertension Red hypertension however occurs also without them Impressed by the frequency of their coexistence Jores[67] and also Wallgren suggested that the hypertension and the vessel changes were coördinated phenomena Thus our problem becomes the demonstration of their common cause

In regard to the bloodvessel changes a twofold or even multiple increase in the thickness of the internal elastic layer in the prearterioles is recognized as a senile phenomenon It might be looked

upon as the forerunner of arteriosclerosis and termed "presclerosis" Where degenerative changes, lipoid deposits and hyalinization are present one [illegible]

causative agents

What do we know about the cause of red hypertension? As in regard to arteriosclerosis in general, so also here all possible exogenous factors like alcohol, overeating, nicotine syphilis psychic disturbances, etc, have been suspected as causes, but without sufficient proof The only etiological factor about which there can be no doubt is age, *viz*, the summit and decline of life The fact that red hypertension is predominantly a disease of old age is usually not being sufficiently stressed It very seldom occurs before the age of thirty, rarely before forty years, frequently between forty and fifty, and most commonly between fifty and seventy years Women are affected nearly as often as men Perhaps the red hypertension in women begins a little later than in men In both sexes it is most frequently found between fifty and sixty years, between sixty and seventy years it is more common in women than in men Table 45 and Figure 89 show the age and sex distribution of 719 patients with red hypertension in the writer's material

TABLE 45 —AGE AND SEX DISTRIBUTION OF RED HYPERTENSION

Age	Men		Women		Total	
	No	Per cent	No	Per cent	No	Per cent
-20			2	0 7	2	0 3
21-30	6	1 5	1	0 3	7	1 0
31-40	27	6 3	15	5 1	42	5 8
41-50	87	20 6	62	20 8	149	20 7
51-60	160	37 9	92	30 9	252	35 0
61 70	109	25 8	88	30 0	197	27 4
71-80	32	7 6	34	11 4	66	9 2
81	1	0 2	3	1 0	4	0 5
	422 (58 7 per cent)		297 (41 3 per cent)		719 (100 per cent)	

[illegible] rience heredity, [illegible] emphasized by [illegible] [17] that one feels inclined to credit the existence of a hypertensive constitution Thus one is led to consider either a tendency to an abnormal vasomotor tone during the declining period of life or an inherited low resistance of the bloodvessel system Those who emphasize the constitutional factor usually assume an abnormal excitability of the vascular system The author leans more toward the assumption of an inferiority of the vascular system, manifested perhaps through an early vasoneurosis It is, however, possible that the wear and

tear of a normal vascular system becomes accelerated through an inherited vasolability, expressing itself by abnormally strong and

the abnormal vascular excitability rather acquired and caused by the unknown mechanism of the red hypertension?

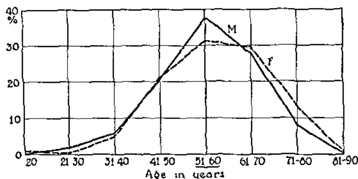


Fig 89 —Age and sex distribution of 719 patients with red hypertension Males 59 per cent females 41 per cent

The author does not consider gout or diabetes of causative impor-

diabetes are coordinated phenomena

At present old age and heredity remain the only important etiological factors and this must not be overlooked in the search for the mechanism of red hypertension Pal[71] has offered the

most important factors of age and constitution Let us rather inquire into the effect of old age upon the vascular system Morphologically there takes place an augmentation of the elastica and of the connective tissue of the arterial wall functionally there is a diminution of extensibility This has been proven for the aorta and the large arteries Is it probable that the smaller arteries, in which the hypertrophy of the elastica is most apparent, remain free from this functional alteration?

The following considerations lead to the recognition of two clinical types of old age changes in the arterial system (1) If the diminu-

tion in extensibility predominantly *affects the aorta* and the larger arteries, the "wind chamber" function of the vascular system will change in such a way that the normal volume output of the h

show a greater lability than the diastolic (2) If the diminution in extensibility affects the smaller arteries chiefly, the systolic widening becomes diminished and the outflow resistance *increased* A greater elevation of the diastolic pressure results and this elevation will show less lability In both types, the blood-pressure will be greatly influenced by the minute volume of the heart In the second type the blood, if its viscosity is increased, will meet with greater friction in the unyielding fine vessels and tend to raise the pressure In neither type is it necessary to assume a changed tone of the arterioles nor a constant stimulation of the vasomotor center nor a central regulation of the pressure at an elevated level

We are familiar with the first clinical type As early as 1913 the author called attention to the fact that in the presence of a low diastolic pressure an increased pulse amplitude may constitute the only sign betraying arteriosclerosis of the aorta and large vessels, other condi
arterioveno
been exclu
amplitude
dominantly
tensive material with the result reproduced in Table 46 Among "systolic hypertensions" Fineberg includes patients with systolic

TABLE 46 — SYSTOLIC HYPERTENSION (FINEBERG)

Age	No of hypertensive patients	Systolic hypertension	Per cent
Below 40	15	0	0
40–49	34	3	9
50–59	83	15	18
60–69	70	29	41
70–79	23	12	52
Over 80	12	7	58

strates a dominant increase of systolic pressure as a pronounced phenomenon of advanced age Ten instances were necropsied, all showing marked generalized atheromatosis and vascular renal changes characteristic of hypertension Heart hypertrophy was absent in one-half of the number of cases and when present, usually not pronounced Fineberg considers systolic and diastolic hyper-

tension to be due to one factor, which causes a constriction of the peripheral vessels, and that a second factor must be added, which lowers the diastolic pressure this factor being atherosclerosis of the larger arteries The author believes that the senile diminution of the elasticity of the large vessels and their atherosclerosis suffice to bring about this characteristic systolic hypertension

The second clinical type with elevation of both systolic and diastolic pressures and marked decrease of dilatability of the small arteries may be identified as red hypertension

There are individuals whose vessels are predestined to grow old early One might picture the process which causes the diminution in elasticity as follows During youth the blood pressure is carried exclusively by the smooth muscles which allow the vessels to dilate and contract within wide limits The elastica safeguards against overdilatation With advancing age and a gradual and insensible stretching of the muscles the elastic elements of the vessel wall are called upon more and more often A hypertrophy of the elastica and an increase in the connective tissue result The more the elastica has to bear the pressure the more the active dilatability ceases, the passive dilatability of the elastica is intrinsically limited This decreased dilatability occurring in youthful vessels at very high pressures only is present in old vessels at slight pressure elevations When this diminution in dilatability affects larger areas of the vascular system and particularly the smaller arteries diastolic pressure increase results from the difficulty in outflow The wall of a severely dilated vessel might set up an increased vascular tone which will lead to muscular hypertrophy in vessels with powerful muscular coat and generally in vessels in which muscular insufficiency has not yet developed

It is hardly necessary to add that the mechanism of the diastolic pressure in red hypertension is more complicated than this mechanical discussion indicates May it suffice to point out that fever for instance will lower a high pressure But attempts to base our ideas upon morphological facts cannot be dispensed with Particularly in tissues which are mechanically used form and function are so closely associated that one cannot be comprehended without the other

Hueck[illegible] looks upon a certain degree of muscular and elastic hypertrophy of the arterial system as a constant result of every high pressure Dietrich's studies[illegible] of the changes in the larger arteries taking place with advancing age brought out important differences between the primary (the author's red) and the secondary nephritic (the author's pale) hypertension With advancing age a decrease of the internal muscle layer and an increase of elastic and collagen fibers occur whether hypertension is present or not In the nonhypertensives the disappearance of muscular fibers is slight irregular

and disseminated In red hypertension the disappearance of muscular elements is diffuse and more marked as is the increase in elastic and collagen fibers There is also with great regularity a hypertrophy of the outer muscular coat and of the remaining fibers of the internal layer and finally a distinct dilatation of the vessel In pale hypertension Dietrich found the same muscular hypertrophy but irregular and disseminated the diminution of the internal muscular layer was lacking and the lumen only slightly widened Lead hypertension showed similar changes The findings were definite enough
studies of the ar
morphological c
two forms of hypertension

The changes in red hypertension just described indicate an elevated tonus in response to the stretching caused by hypertension The absence of dilatation and the more obvious hypertrophy of the better preserved internal muscular layer in nephritic hypertension may easily be correlated with the chemical mechanism of active vasoconstriction indicating that here we are dealing with hypertension caused by hypercontraction

In red hypertension elastica defects are never missed in early changes of the media Quite similar changes are also found in the arteries of the lower extremities in young people without hypertension This might point to dilatation and fatigue of the tissue as a primary factor We assume that the dilatation is accompanied by an increased mu
muscle coat in the la
the smallest arteries
a hypertrophy of the e
of increasing the peri
This again leads to increased stretching and instead of a purposeful compensatory mechanism we have actually a vicious circle

It has already been mentioned that in essential hypertension marked elastic hypertrophy is to be found in special vascular areas particularly in the abdominal organs and most frequently in the kidneys Johnson (1868) and Ewald (1877) early described hypertrophy of the media in the smallest arteries yet lately relatively less attention has been given to this phenomenon Fahr in 1922 called attention to the greatly reduced media in the renal vessels as compared with the well developed musculature of the small arteries of the skin the intestines and particularly the skeletal muscles Kernohan Anderson and Keith[68] on biopsy material from the pectoral muscle of patients with hypertension have demonstrated a distinct muscular hypertrophy of the arterioles Normally the ratio between wall thickness and lumen according to these authors averages 1 to 2 (1 to 1 7 to 1 to 2 7), in benign hyper

tension the ratio is distinctly higher, averaging 1 to 1 4 (1 to 1 1 to 1 to 1 8) and in malignant hypertension this change was still more pronounced

Another important and nearly constant morphological finding in red hypertension is the so-called *arteriolosclerosis* Different authors have offered different interpretations (1) as the common form of the arteriosclerosis of the arterioles (2) as the sought-for organic resistance which forces the pressure to rise (3) as the result of the excessive load imposed by the high pressure

The first interpretation the author does not consider correct The second alternative likewise can be dismissed because arteriolosclerosis is never found diffusely in wide areas of the vascular system but nearly always in the abdominal organs only, with marked predilection for the kidneys

However is not the fatty and hyaline degeneration of the arterioles which we name arteriolosclerosis at least responsible for the disturbed blood supply of the renal units bringing about their destruction and thus producing the granulated kidney of red hypertension? Most authors answer this question in the affirmative But such an explanation is not well founded As Hueck[56] has pointed out what closes the arterioles is a soft mass which would yield to pressure We deal with *arteriolomalacia* rather than arteriolosclerosis and the changes must be the result of disturbed blood supply perhaps of a slowing of the circulation If one accepts

pressure did not suffice to overcome the resistance so as to provide the terminal vascular structures with sufficient circulation As shown by Hauch and especially by Baehr and Ritter[57] roentgen ray films of hypertension kidneys injected with barium reveal that not all large middle-sized and small arteries have filled but the entire vascular tree is rarefied On the other hand Ricker as well as Sywall[74] have shown that it is possible to inject hyaline arterioles which from their microscopic appearance were almost completely occluded Arteriolomalacia to the author is a sign of disturbed blood supply present in red hypertension only when marked hypertrophy of the elastic layer is simultaneously present in the prearterioles With it is associated a diminution of active and passive dilatability of the prearterioles and in this he sees the cause of the disturbed blood supply It is the cause of the degeneration and obliteration of the arterioles and of the regressive changes of the glomeruli That identical arteriolar changes occur in chronic nephritis is an additional fact in support of the conception that disturbance of blood supply is the cause not the result of arteriolosclerosis or

arteriolomalacia In nephritis there can be no doubt that serious

for
the high pressure is easily derived from the above The swollen wall of the arterioles indicates that the wall is no longer exposed to the high pressure existing within the larger ramifications of the arterial system Arteriolomalacia follows upon high blood pressure but its cause is the diminution of circulation which results from the diminished dilatability due to elastica hypertrophy or abnormal muscular tone of the prearterioles senile or presenile changes of a constitutionally weakened vascular system

In contrast to the active mechanism of vasoconstriction in pale hypertension we might speak of a *passive mechanism of red hypertension* Passive insofar as we consider an overstretching of the arterial system the cause of the process The isolated increase in systolic pressure the author likes to explain on the basis of the diminished elasticity of the large arteries The increase in peripheral resistance which causes the elevation of the diastolic pressure may perhaps be explained in the following way The overdistention and hardening of the small arteries lead to a stretching of the

To this abnormal demand for distention the most minute arteries answer reflexly with increase of muscular tone and hypertrophy and thus bring about an increase in peripheral resistance They are not in a stage of vasoconstriction but they have changed into a rigid system with a permanent tone preventing normal rhythmic relaxation

This abnormal tone might well express itself also in the pathological excitability described as the hypertonic reaction type of the arterial system which most authors look upon as inherited

sclerotic process we find the hypertonic diabetes of old age

To summarize the discussion so far carried out the concept of a passive mechanism of red hypertension is based upon the assump-

stretching all processes commencing while a normal pressure still

exists and followed by an increased tonus of the arterioles *via* vasovascularis reflex

Another reflex mechanism may be thought of, a vasoneural reflex one over the so-called *Blutdruckzugler*, the depressor and sinus nerves Contrary to what is frequently observed in the pale hypertension of nephritis red hypertension is not accompanied by a slowing of the pulse rate One even observes patients usually with very high pressure and an unfavorable prognosis, in whom the rate stays above 90 What is then in red hypertension the rôle of the *Blutdruckzugler?* Evidently their receptor organs in the arterial wall are no longer responsive to the normal stimulus of intravascular pressure Except for the receptors the reflex arc is capable of function as proved in some instances through the lowering of blood pressure following outside pressure upon the carotid sinus, as demonstrated by Hering [64] It is inviting to correlate the lack of sensitivity of the receptors in the vessel walls with the decreased arterial dilatability discussed above The condition as it exists might be considered as a decreased tone of the Blutdruckzugler and compared with the experimental results when this tone is abolished by the section of the depressor and sinus nerves, an operation resulting in sustained hypertension (Hering Heymans) What happens under these circumstances to the hormonal stimulation unavoidable as a part of splanchnic stimulation? Heymans has ascribed to the carotid sinus a regulatory influence upon the secretion of adrenalin Goormaghtigh and Elaut,[62] of the same university as Heymans have studied the effects of this experimental hypertension upon the suprarenals The section of the nerves results in

within a f

exhaustion

findings indicate a constant hyperfunction of the medulla and clearly demonstrate marked thickening of the cortex, caused by greatly increased cholesterol content

One might well say that compared with other known internal secretions adrenalin possesses the most prompt and violent action, as demonstrated perhaps most strikingly through its effect upon metabolism (Boothby and others) The suprarenal veins thus function as the excretory ducts for a powerful and dangerous secre-

secin ... irregularly arranged ...

the

is su

vein

zieher) From either viewpoint the mighty muscular hypertrophy

arteriolomalacia In nephritis there can be no doubt that serious circulatory disturbance is present as a result of vasoconstriction

The author's position in regard to the third interpretation offered for arteriolosclerosis *as the result of the excessive load imposed by* the high pressure, is easily derived from the above The swollen wall of the arterioles indicates that the wall is no longer exposed to the high pressure existing within the larger ramifications of the arterial system Arteriolomalacia follows upon high blood-pressure but its cause *is the diminution of circulation, which results from* the diminished dilatability due to elastica hypertrophy or abnormal muscular tone of the prearterioles, senile or presenile changes of a constitutionally weakened vascular system

In contrast to the active mechanism of vasoconstriction in pale hypertension, we might speak of a *passive mechanism of red hypertension* Passive, insofar as we consider an overstretching of the arterial system the cause of the process The isolated increase in systolic pressure the author likes to explain on the basis of the diminished elasticity of the large arteries The increase in peripheral resistance which causes the elevation of the diastolic pressure may perhaps be explained in the following way The overdistention and hardening of the small arteries lead to a stretching of the

answer reflexly with increase of muscular tone and hypertrophy, and thus bring about an increase in peripheral resistance They are not in a stage of vasoconstriction but they have changed into a rigid system with a permanent tone preventing normal rhythmic relaxation

This abnormal tone might well express itself also in the pathological excitability, described as the hypertonic reaction type of the arterial system, which most authors look upon as inherited, but which rather might be acquired We might properly speak of an *angiosclerosis*, signifying something different from atherosclerosis, hardening only of the wall of the small arteries accompanied by elastica hypertrophy, which diminishes its active and passive dilatability Where the pancreas is seriously affected by the angiosclerotic process, we find the hypertonic diabetes of old age

To summarize the discussion so far carried out, the concept of a passive mechanism of red hypertension is based upon the assump-

stretching all processes commencing while a normal pressure still

exists, and followed by an increased tonus of the arterioles *via* vaso-vascularis reflex

Another reflex mechanism may be thought of, a vasoneural reflex one over the so-called *Blutdruckzugler*, the depressor and sinus nerves Contrary to what is frequently observed in the pale hypertension

a slowing of

with very high

he rate stays

above 90 What is then in red hypertension the rôle of the *Blutdruckzugler?* Evidently their receptor organs in the arterial wall are no longer responsive to the normal stimulus of intravascular pressure Except for the receptors the reflex arc is capable of function, as proved in some instances through the lowering of blood pressure following outside pressure upon the carotid sinus, as demonstrated by Hering[64] It is inviting to correlate the lack of sensitivity of the receptors in the vessel walls with the decreased arterial dilatability discussed above The condition as it exists might be considered as a decreased tone of the Blutdruckzugler and compared with the experimental results when this tone is abolished by the section of the depressor and sinus nerves, an operation resulting in sustained hypertension (Hering, Heymans) What happens under these circumstances to the hormonal stimulation unavoidable as a part of splanchnic stimulation? Heymans has ascribed to the carotid sinus a regulatory influence upon the *secretion of adrenalin Goormaghtigh and Elaut[62] of the same* university as Heymans, have studied the effects of this experimental hypertension upon the suprarenals The section of the nerves results in an immediate stimulation of suprarenal activity, visible within a few hours in greatly reduced chromaffinity This acute exhaustion is overcome After four months of hypertension the findings indicate a constant hyperfunction of the medulla and clearly demonstrate marked thickening of the cortex, caused by greatly increased cholesterol content

One might well say that compared with other known internal secretions adrenalin possesses the most prompt and violent action, as demonstrated perhaps most strikingly through its effect upon metabolism (Boothby and others) The suprarenal veins thus

pretation having been given Against the assumption that these

arteriolomalacia In nephritis there can be no doubt that serious circulatory disturbance is present as a result of vasoconstriction

The author's position in regard to the third interpretation offered for arteriolosclerosis as the result of the excessive load imposed by *the high pressure, is easily derived from the above The swollen* wall of the arterioles indicates that the wall is no longer exposed to the high pressure existing within the larger ramifications of the arterial system Arteriolomalacia follows upon high blood pressure but its cause is the diminution of circulation, which results from the diminished dilatability due to elastica hypertrophy or abnormal muscular tone of the prearterioles senile or presenile changes of a constitutionally weakened vascular system

In contrast to the active mechanism of vasoconstriction in pale hypertension, we might speak of a *passive mechanism of red hypertension* Passive insofar as we consider an overstretching of the *arterial system the cause of the process The isolated increase in* systolic pressure the author likes to explain on the basis of the diminished elasticity of the large arteries The increase in peripheral resistance which causes the elevation of the diastolic pressure may perhaps be explained in the following way The overdistention and hardening of the small arteries lead to a stretching of the smallest arteries which ordinarily are not subjected to this stretching process because normally the elastic capacity of the arteries lying farther upstream transform the pulsating stream to a uniform flow To this abnormal demand for distention the most minute arteries

rigid system with a permanent tone preventing normal rhythmic relaxation

This abnormal tone might well express itself also in the pathological excitability, described as the hypertonic reaction type of the arterial system which most authors look upon as inherited but which rather might be acquired We might properly speak of an *angiosclerosis,* signifying something different from atherosclerosis, hardenin

by elastica h

dilatability

sclerotic process we find the hypertonic diabetes of old age

To

passi

tion (

of its different structural units, microscopically visible in ...

of the internal muscular layer, defects in the elastic layer and overstretching all processes commencing while a normal pressure still

exists and followed by an increased tonus of the arterioles via vaso-vascularis reflex

Another reflex mechanism may be thought of a vasoneural reflex one over the so-called *Blutdruckzügler* the depressor and sinus nerves Contrary to what is frequently observed in the pale hypertension of nephritis red hypertension is not accompanied by a slowing of the pulse-rate One even observes patients usually with very high pressure and an unfavorable prognosis in whom the rate stays above 90 What is then in red hypertension the role of the *Blutdruckzügler*? Evidently their receptor organs in the arterial wall are no longer responsive to the normal stimulus of intravascular pressure Except for the receptors the reflex arc is capable of function as proved in some instances through the lowering of blood pressure following outside pressure upon the carotid sinus as demonstrated by Hering[61] It is inviting to correlate the lack of sensitivity of the receptors in the vessel walls with the decreased arterial dilatibility discussed above The condition as it exists might be considered as a decreased tone of the Blutdruckzügler and compared with the experimental results when this tone is abolished by the section of the depressor and sinus nerves an operation resulting in sustained hypertension (Hering Heymans) What happens under these circumstances to the hormonal stimulation unavoidable as a part of splanchnic stimulation? Heymans has ascribed to the carotid sinus a regulatory influence upon the secretion of adrenalin Goormaghtigh and Elaut[62] of the same university as Heymans have studied the effects of this experimental hypertension upon the suprarenals The section of the nerves results in an immediate stimulation of suprarenal activity visible within a few hours in greatly reduced chromaffinity This acute exhaustion is overcome After four months of hypertension the findings indicate a constant hyperfunction of the medulla and clearly demonstrate marked thickening of the cortex caused by greatly increased cholesterol content

One might well say that compared with other known internal secretions adrenalin possesses the most prompt and violent action as demonstrated perhaps most strikingly through its effect upon metabolism (Boothby and others) The suprarenal veins thus function as the excretory ducts for a powerful and dangerous secretion Attention has long been focussed upon the peculiar muscular arrangements in the walls of these veins without a convincing interpretation having been given Against the assumption that these seemingly irregularly arranged longitudinal muscle bundles serve in the expression of adrenalin from the glands the opposite function is suggested that through contraction they affect the lumen of the veins and regulate or tend to regulate the rate of discharge (Goldzieher) From either viewpoint the mighty muscular hypertrophy

of the s preson l l
tio

of cause and effect in hypertension

The problem of the so-called *malignant hypertension* or malignant nephrangiosclerosis will finally be considered

As long as the passive mechanism of red hypertension prevails renal insufficiency does not occur We are dealing with a benign disease insofar as the kidneys are concerned a benign nephrangiosclerosis and we distinguish a cardiac cerebral or pancreatic course of the cond t on In a n mb

course leads to renal insufficiency and true uremia the genuine contracted kidney The sudden turn in the course of the disease has never been fully understood The consideration of a typical instance brings out the differences from red hypertension The patient is pale the capillaries extremely contracted the eyegrounds frequently reveal the first sign of the fatal turn in form of contracted arteries and the classical picture of retinitis angiospastica Histologically the kidneys show the same characteristic ischemic reactions as in acute and subacute nephritis Particular attention is called to the small arteries where inside the hypertrophic elastic layer one finds the endarteritis obliterans which is characteristic of the active mechanism of vasoconstriction It consists of endothelial proliferation and an increase of subendothelial connective tissue as in vascular occlusion changes not observed in red hypertension The endarteritis and the occasionally coexisting arteriolonecrosis are definite histological signs of marked arterial constriction Vasoactive pressor substances are found in the blood prior to any demonstrable impairment of renal function The blood pressure is increased above the level of the red hypertension particularly the diastolic The angiospastic closure of the vessels leads to the death of numerous glomeruli with destruction of secretory units all
con
con
ressor

substances in circulation

In regard to the cause of this fatal turn at present the following only might be said The cause cannot be found in impaired renal function since retinitis angiospastica as already stated frequently occurs earlier than any demonstrable decline of function Bohn in a group of patients found pressor substances even before the occurrence of retinitis The clinical course proved these instances as intermediary cases Though the histological findings make the disturbance of renal blood supply a certainty the elastic hyper

trophy in the smaller arteries already discussed do not constitute the most important histological change As such the author is inclined to recognize the muscular hypertrophy

The age of the patient and the height of the diastolic pressure seem to be factors of special importance The younger the individual in whom a genuine hypertension has developed and the higher his diastolic pressure, the greater is the danger of a malignant course In contradistinction to the sex distribution of red hyper-

TABLE 47 —AGE AND SEX DISTRIBUTION OF MALIGNANT HYPERTENSION

Age	Men		Women		Total		
	No	Per cent	No	Per cent	No	Per cent	Per cent *
20							0 3
21–30	2	1 6			2	1 3	1 0
31–40	17	13 8	4	11 8	21	13 3	5 8
41–50	45	36 6	14	41 3	59	37 6	20 7
51–60	47	38 2	10	29 3	57	36 3	35 0
61 70	9	7 3	5	14 7	14	9 0	27 4
71–80	3	2 5	1	2 9	4	2 5	9 2
	123 (78 3 per cent)		34 (21 7 per cent)		157 (100 per cent)		

* Red hypertension (from Table 45)

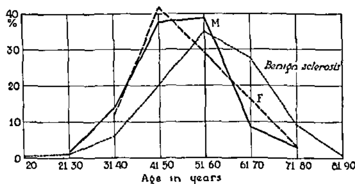


FIG 90 Age and sex distribution of 157 cases of malignant hypertension Males 78 per cent females 22 per cent

men and 22 per cent women as *versus* 59 and 41 per cent for red hypertension The frequency among both men and women is high in the age groups forty-one to fifty and fifty-one to sixty, but drops off rapidly toward both sides Between sixty-one and seventy years there seems to be relatively fewer men than women with malignant

hypertension Fig 90 for comparison also contains the age distribution for the *total red hypertension* material The curve for red hypertension is pushed forward just a decade later in life than the curves for malignant hypertension If we pool out whole material of genuine *hypertension, benign and malignant* we possess records of 876 patients, of which 157, or 18 per cent, presented a course characterized by retinitis angiospastica or renal insufficiency In the whole material there were *545 men and 331 women Of the men* 22 per cent progressed toward renal insufficiency, of the women 10 per cent

An accurate understanding of the *malignant sclerosis will* be possible only when we understand better the occurrence of pressor substances in the blood We used to look upon this condition as a [illegible] ept [illegible] We [illegible] on, [illegible] he hematogenous hypertensive mechanism to the passive mechanism *of red hypertension*

High blood pressure is frequently looked upon as a symptom like fever The high pressure from hyperadrenalinemia in certain suprarenal tumors may be considered a symptom of suprarenal hyperactivity red hypertension as a symptom of general or splanchnic angiosclerosis while in malignant sclerosis the pale hypertension is not a mere symptom, but the cause of the fatal disease, it is the cause of the contracted kidney

One frequently looks upon hypertension as a compensatory mechanism to increase the blood supply of the kidneys In pale hypertension according to the concept developed in this treatise, there *can be no question of any compensatory* benefit derived from the high pressure The general vasoconstriction includes all the danger which threatens the kidney *could* the production of pressor substances be checked the prognosis would be fundamentally altered

In regard to red hypertension the question is more difficult to answer *If one accepts the assumption of a decreased arterial dilatability* as the cause of the pressure elevation, the blood-pressure increase becomes significant as a compensatory mechanism *Through it is secured a normal* nutrition of the organs involved *Is it not the cause of the favorable span of life* and the practically normal capacity of these individuals? Would not *the blood supply* to the kidneys as well as to other organs suffer if the insufficiency of the peripheral pumping mechanism of the small arteries were not compensated *for by a high pressure and increased* work by the heart?

According to Thoma's[75] and our own (Donecke and Rothschild [9]) *investigations the vascular* resistance of the kidney can be appre-

ciably raised As the renal vessels form more and more elastic tissue to replace disappearing musculature they become less and less capable of dilatation and the free vasomotor play diminishes the renal blood supply will more and more depend on the blood pressure and this as experience teaches becomes more stable at a high level

The utility of this apparent compensatory arrangement becomes doubtful when one considers the minor vascular changes in the kidneys to be the result of the wear under not more than normal pressure and their further development and the increased tone of the arterioles to be the result of vascular hyperdistention With this chain of events in mind we realize that we are concerned with the existence of a vicious circle rather than of a compensatory mechanism

References

General and Introduction

1 Anrep G V 1912 On the part played by the suprarenals in the normal vascular reactions of the body J Physiol 45 307–317

2 ——— 1924 A new method of crossed circulation Proc Roy Soc B 97 444–449

3 Anrep G V and Daly I de Burgh 1924 The output of adrenaline in cerebral anemia as studied by means of crossed circulation Proc Roy Soc B 97 450–463

4 Anrep G V and Segall H N 1926 The central and reflex regulation of the heart rate J Physiol 61 215–231

5 Anrep G V and Starling E H 1924 Central and reflex regula

tem Handb

d norm u

vascular reflexes

ved in the reflex

lerose Handb d

erz und Gefasse

ogène regulatrice

oned re ve J Am Med Assn 89 104 1050

20 Tournade, A 1928 Les sécrétions internes Les capsules surrénales, *in* Traité de physiol norm et pathol, by Roger et Binet, 4, 457

21 Tournade, A, and Chabrol, M 1921 Technique des circulations

fets vaso-constric
Compt rend Soc

23 Tournade, A, Chabrol, M, and Marchand, H 1921 Des mécanismes nerveux régulateurs de la pression artérielle I La régulation centrale

25 ———— 1923 Der arterielle Hochdruck, Verhandl d deutsch Gesellsch f inn Med, 35, 134–175

26 ———— 1925 Uber die chirurgische Behandlung der Nephritis, Klin Wchnschr, 4, 145–151

27 ———— 1926 *In* 'Hypertension, Leipzig, Georg Thieme

28 Volhard, F, and Fahr, Th 1914 Die Bright sche Nierenkrankheit Berlin, Julius Springer

29 Volhard, F, and Hulse, T 1923 Zur Frage der Blutdrucksteigerung Der Adrenalingehalt des Blutes bei der Blutdrucksteigerung durch Splanchnicusreizung und durch Asphyxie, Ztschr f exp Med, 38, 524–527

Pale Hypertension

30 Albrecht, H U, and von Brochowski, A 1928 Uber die Bedeutung der Serumeiweisskorper fur Tonusschwankungen der Gefassmuskulatur, Ztschr f klin Med, 107, 256–279

31 Alder, A E 1921 Über die Ursachen und die Therapie der Hypertonie bei den Nephritiden mit einem Beitrag zur Pathogenese der akuten Nephritis, Schweiz med Wchnschr, 51 713–719

32 Becher, E, and Herrmann E 1925 Ueber freie und gebundene Aminosaure im Blut bei Niereninsuffizienz, Munchen med Wchnschr, 72 1069–1070

33 Bodenstab, Ella 1928 Uber vasoconstrictorische Substanzen im fliessenden Blut, Ztschr f exp Med, 63, 758–766

34 Bohn, H 1930 Mechanismus des blassen Hochdrucks, Verhandl d deutsch Gesellsch f inn Med, pp 198–202

35 Curtis, F R, Moncrieff, A A, and Wright, S 1927 The sup- od

39 ———— 1922 Zur Frage der Blutdrucksteigerung I Experimentelle Untersuchungen über die Bedingungen der Adrenalinwirkung Ztschr f exp Med 30, 240–267

43 ———— 1926 Zur Frage des essentiellen Hochdrucks, Munchen med Wchnschr, 73(2) 2110–2114

44 HULSE W AND FRANKE K 1929 Weitere Untersuchungen zum Chem smus der nephritischen Blutdrucksteigerung Arch f exp Path u Pharmakol 143 257 268
45 HULSE W AND STRAUSS H 1924 Zur Frage der Blutdrucksteigerung Uber die Wirkung hoherer Eiweissspaltprodukte auf den Blutdruck und ihr Vorkommen im Blute bei hypertonischen Nierenkrankheiten, Ztschr f exp Med 39 426–461
Serums
Exp
ularen
1258–
48 MAJOR R H 1925 The possible relationship between guanidine and
pertension Am
ncrease of guani
Int Med 40
831–899
51 ——— 1927 Probable presence of increased amounts of guanidine in the blood of patients with arterial hypertension Bull Johns Hopkins Hosp 40 85–89
52 TASHIRO S 1926 Sensitization of sympathetic system by serum from
L
R d Hyperte sion
56 ALLEN E V 1929 The suprarenal glands and hypertension a study
59 DONECKE F AND ROTHSCHILD P 1927 Uber das Verhalten der postmortalen Durchstromungskapazitat des Blutgefasssystems der Niere bei Erkrankungen mit und ohne Blutdrucksteigerung Zentralbl f inn Med 48 866–877
60 FINEBERG M H 1927 Systolic hypertension its relation to athero sclerosis of aorta and larger arteries Am J Med Sci 173 835–843
61 GOLDZIEHER, M A AND SHERMAN I 1928 Hypertrophy of muscle in suprarenal vein Arch Path 5 1 12
62 GOORMAGHTIGH N AND ELAUT L 1929 Histophysiologie de la sur rénale pendant l hypertension artérielle experimentale Compt rend Soc de biol 101 501–504
63 HAUCH 1913 Die Arterien der gesunden und kranken Niere im Rontgenbild Fortschr Rontgenstr 20 172 182

68 KERNOHAN, J W, ANDERSON, E W, AND KEITH, N M 1929 The Arterioles in cases of Hypertension, Arch Int Med, 44, 395–423

69 MAHOMED, F A 1874 The etiology of Bright's disease and the prealbuminuric stage, Med Chir Trans, 57, 197–228

70 PAL, J 1925 Hypertonie und Hypertension, Wien klin Wchnschr, 38, 414–415

71 ———— 1928 Klinik und Therapie des arteriellen Hochdruckes, Med Klin, 24, 123–126, 166–167

72 RICKER, GUSTAV 1927 Sclerose und Hypertonie der innervierten [illegible]

CHAPTER XXIV

BILATERAL NECROSIS OF THE RENAL CORTEX *

By WALTER DE M SCRIVER M D

Incidence —Bilateral necrosis of the renal cortex, also described as symmetrical necrosis or bilateral infarction, was apparently first described in 1886 by Juhel-Rénoy In a search of the literature the author has been able to find 38 other cases which fall into this group Four of these recovered so that pathological specimens were not obtained, but the clinical picture is so definite that it appears that up to a certain level the same process was present in all

CASE HISTORIES In recent years the author has seen in the clinics at the Royal Victoria Hospital 3 cases of this type, with death and autopsy confirmation in 2 and recovery in 1 All were admitted to the Maternity Service, where they were observed at the request of the attending obstetricians The pathological studies which are reported here in brief were made by Professor Oertel, to whom the author is indebted for permission to use them

and erythrocytes

* The first three cases described here have been reported in detail with Horst Oertel in the Journal of Pathology and Bacteriology 33 1071 1094 1930 under the title Necrotic Sequestration of the Kidneys in Pregnancy (Symmetrical Cortical Necrosis)

the hospital She was delivered of a dead fetus and the placenta was followed by a large old blood clot For three days the

TABLE 48 —CASE 1

Day post partum	Urine volume cc	Blood urea mg per 100 cc	Blood creatinine mg per 100 cc	Blood-pressure
1	60			
2	11	53	2 47	160/110
3	1			160/100
4	0	125	4 28	145/100
5	0	154	4 0	135/95
6	0			140/90
7	0			135/85
8	0	171	6 60	
9	0			
CASE 2				
1	450			
2	1300			
3	550			
4	0	195	6 5	140/75
5	0			135/80
6	0	191	6 4	125/60
7	3	239		140/60
8	0			160/80
9	0			

Th

in

rha

spe

alb

was

admission spontaneous abortion took place Immediately after delivery she was given a blood transfusion which was followed by jaundice of less than twenty four hours duration Repeated tests of the donor s and patient s bloods failed to show any evidence of incompatibility and no hemoglobinuria was present Oliguria with increasing nitrogen retention and failure of renal function developed (Table 49) followed by increased

found completely free from protein

In all 3 cases the clinical picture was such as to suggest surgical obstruction of the urinary tract and cystoscopic examination with catheterization of the ureters was performed in each case with negative results

TABLE 49 —CASE 3

Day postpartum	Urine					Blood chemistry mg per 100 cc		Blood pressure
	Volume cc	Specific gravity	Albumin	R B C	Urea per cent	N P N	Creatinine	
1	425	1008	+	+				
2	160							
3	320							
4	410	1008	•					110/70
5	380					104	4 6	
6	480					91	4 8	120/75
7	540	1008	+	+	0 21			
8	1020				0 23	67	6 0	135/70
9	1630		+		0 22			
10	2550				0 23	80	6 4	
11	3500				0 25			150/70
12	2600				0 [illegible]0			154/75
13	2900				0 29	82	5 4	130/70
14	2370				0 40			
18	1780					71	1 9	105/76
25	1300	1018	Faint trace	0		42	1 4	110/70
30	1300	1020	Faint trace	0		27	1 4	110/70

These 3 cases, in common with those which the author has been able to find in the literature present a distinct clinical picture Out of altogether 41 observed instances (26 including the author s, reported since 1920), 33 occurred in women, 5 in males and 3 in children Among the 8 cases not occurring in women, 1 instance followed diphtheria and 3 dysentery In all women the condition was connected with pregnancy, in 3 instances with miscarriage as early as in the fourth month, once in the fifth month, in the remainder later, usually near or at full term Fourteen times the pregnancy was complicated by retroplacental hemorrhage Convulsions occurred in 11 instances, either before, during or after the delivery in 1 case as late as on the seventeenth day In the author s first case where in the thirteenth pregnancy abortion took place in the third month, and in the fourteenth pregnancy miscarriage in the sixth month, the heart, at autopsy, proved hyper- [illegible]

[illegible]

the duration of at least a couple of weeks In 15 instances, edema of greater or lesser degree preceded the onset of urinary suppression With these exceptions, there may be absolutely no clinical signs or history to suggest renal involvement or toxemia beforehand The anuria in the majority of cases was almost complete, coming on

immediately or up to five days after the delivery In general the duration of life was proportional to the amount of urine secreted, with complete anuria, death usually *occurred on the eighth or ninth* day The urine always contained protein and usually erythrocytes Very few chemical observations were made on the blood, the ones available revealed only a rapid rise of the non-protein nitrogen, especially of the creatinine Blood pressure observations were available in surprisingly few cases, the more recent not excepted, and in

Among

between

120 mm

in the

detailed information there was a tendency for the pressure to drop as the disease progressed, though the author s second case showed a different course Attention should particularly be called to the mode of death As a rule, there was nothing to be seen of grand uremia, neither convulsions nor signs of extreme acidosis, the patient might be mentally clear almost until death occurred

Decapsulation has been performed in a number of cases, *in some* without beneficial results Of the 5 instances including the author s, in which recovery took place, decapsulation was done in 3, while in the remaining 2 including the author's case, the recovery might *be characterized as spontaneous*

Pathology of the Kidneys —The gross microscopic pictures of the kidneys postmortem agreed closely in the author s cases and those described in the literature

In the author s cases the kidneys were somewhat enlarged and swollen On section the outer portion was yellowish, greasy and dots and streaks, t region The whole reddish band, lying

main zones or rather stages of severity of the alterations Though these zones are microscopically readily distinguished and clearly characterized, they are actually not strictly separated, but flow one into the other without sharp demarcation and appear in places almost mingled

1 Irregular pale areas in a state of advanced tissue dissolution necrosis The cells *s of lysis,*

their pycnotic nuclei occasionally visible The glomeruli, distended within the capsules, enclose fading shadows of red blood cells, leukocytes and detritus The intralobular arteries (Gross[2]) are dilated and thrombosed by agglutinated red and white blood cells within a fibrin network, the process can be traced into some of the afferent glomerular vessels and even into the capillary loops themselves The larger interlobar arteries were free and contained no agglutinated blood cells in the first case, while in the second case the arteries at the cortico-medullary boundary were involved in the process

2 A second zone, not sharply differentiated from the first, presented similar necrotic areas, but was further distinguished by

chyma) There were also blood extravasations into the interstitial tissue spaces

In the author s first case these two zones were further characterized by a unique heavy lipoid infiltration, almost wholly confined to the vascular channels of the cortex The fat was present as

in the tubules—in short, the picture of a severe acute or subacute nephritis Occasional groups of necrotic tubules were scattered here and there The medulla was *moderately* edematous, with irregular streaky tubular and intertubular hemorrhages and abundant casts in the tubules, chiefly hyaline, but also cellular

Etiology —This renal condition has usually been interpreted as a thrombosis of the glomerular and interlobular arterial vessels with consequent necrosis of the infarcted tissue, the thrombosis being ascribed to spasm of all the vessels of the area secondary to some unknown cause It is difficult to understand a spasm of such long duration and the infarcted tissue is too greatly engorged with blood to fit in with such a long-continued spasm On the other hand, it would be difficult to account for those cases which have recovered

outcome

According to Ricker and his co-workers[3, 4] the terminal vascular

segments respond to weak irritation by vasodilatation to medium irritation by vasoconstriction and to strong irritation by vasoparalysis the proximal arteries in this state still being constricted while the terminal arterioles and capillaries are greatly dilated With an increasing degree of the last state there is exudation of serum and leukocytes or even actual hemorrhage by diapedesis and finally complete stasis in the terminal segments (capillaries and arterioles) These observations have been confirmed repeatedly in Professor Oertel s laboratory

The study of the various zones in the kidney described above shows areas corresponding to these different states of vascular irritation If the blood stream be in a state of stasis for a sufficiently long period thrombosis will occur particularly in conditions such as pregnancy where there is a decreased coagulation time and increased sedimentation rate on the other hand if the irritation be removed soon enough the tone of the terminal vascular segments is recovered and a normal blood flow is restored with recovery of the tissues

What the actual cause of the vascular irritation may be is open to conjecture but it is in all probability bound up with the irritability of the vascular system which has been shown to be present in pregnancy and in some infectious diseases

ADDENDUM

Since this communication was prepared in its original form the author has seen and diagnosed during life 2 additional cases of this condition both of which were confirmed at autopsy

The first occurred in a primipara who suffered a retroplacental hemorrhage in the seventh month followed by anuria of seven days duration This patient was seen in consultation at another hospital and no studies were made other than to determine the non protein nitrogen which was at the level of 218 mg per 100 cc

At autopsy the lesion was found to be apparently earlier than those seen in the other cases consisting of numerous large areas of necrosis confluent in some regions grossly discrete in others but limited to the cortex and otherwise resembling the previous cases both grossly and microscopically

The second case occurred in a woman aged thirty years who suffered a retroplacental hemorrhage in the seventh month of her fourth pregnancy In the sixteen hours following delivery 65 cc of urine were recovered by catheter complete anuria ensued for the next thirty six hours after which secretion gradually commenced Death occurred on the tenth day postpartum during this period a total volume of 900 cc being secreted (A summary of the urine volume and blood chemical findings is included in Table 50)

TABLE 50

Day post partum	Urine		Blood chemistry mg per 100 cc		
	Volume	Specific gravity	N P N	Creatinine	Inorganic phosphorus
1	65				
2	0		54 6	2 9	
3	15		109	3 8	7 1
4	40	1 01?	136	5 4	
5	67	1 012	150	6 8	3 3
6	110	1 011	16?	7 7	
7	135	1 011	180	8 8	4 9
8	184	1 01	166	11 5	
9	243	1 012	178	12 0	1 9
10	105	1 012	18_	11 5	5 4

In the microscopic examination of the urine abundant pus cells were found and also an occasional erythrocyte there were no casts Retinal hemorrhages slight in extent developed two days before death which occurred as in the other cases with no frank signs of uremia

In view of the author s theory that the condition is due to vasoparalysis of the terminal vascular segments an attempt was made to overcome this state by hypodermic injections of 0 5 cc of adrenalin chloride solution (1 to 1000) these were followed by transient rises of the blood pressure from the average of 140 systolic and 70 diastolic to a maximum of 200/120 with little apparent effect good or bad

The pathological picture in this case resembled closely that of the first 2 with well marked cortical necrosis grossly and microscopically

It is possibly of interest that Case 3 who recovered is still alive and now four years after the acute condition she has a normal renal function and blood pressure There have been no subsequent pregnancies

In a recent paper Ash[1] has been able to add to the number of cases found in the literature by the author and in addition reports 2 cases of his own occurring in males in which the typical lesion was found at autopsy

REFERENCES

1 ASH J E 1933 Bilateral cortical necrosis of the kidneys (angioneurotic anuria) Am J Med Sci 185 71-87 With bibliography
2 CROSS L 1917 Studies on the circulation of the kidney I J Med Res 36
3 RICKER G 19 1 Die Methode d direkten Beobachtungen d lokalen Kreislaufstörungen Handb d biolog Arbeitsmethoden 8 1
4 ———— 1927 Sklerose und Hypertonie der innervierten Arterien

CHAPTER XXV

RENAL NEOPLASMS *

By STANLEY P REIMANN, M D

GENERAL CONSIDERATIONS OF NEOPLASMS

KIDNEY tumors, like tumors in other situations, demand classification, which is ordinarily done either in anatomical terms relating to adult or embryological anatomical situations, or on the basis of morphology As in congenital anomalies, it is possible, however, to add certain dynamic concepts which help clarify some of the inherent contradictions that no amount of words or classifications or reclassifications in the purely anatomical sense will settle

It seems better, for the purposes of this chapter, to develop parts of this dynamic point of view and attempt to apply it to renal tumors rather than to describe in detail their morphology and other characteristics which are described in many other places [1]

By dynamic concepts in this case is meant application in theory to human tumors of *certain fundamental ideas concerning* what

been used in the majority of cases as the means by which the evolution of animals and plants has been accomplished it is nevertheless *not the only method that has been employed* The group siphonaceous algæ may be mentioned as a class of organisms which have evolved as one gigantic cell, or, by way of the plasmodium route, as it is called [2]

Thus in considering tumors *in general*, we are *confronted with the* problem of what protoplasm can and what it cannot do, what it does and what it fails to do Of course in humans, we must deal primarily with this protoplasm as it is subdivided into cells though plasmodia are also found in humans *The heart muscle develops* as a syncytium there is a syncytium in the deciduæ, and examples are not rare of tumors that take the character more of a plasmodium than of a cellular structure With this reservation then, we will proceed to a few pertinent considerations *of cells in their relation to* tumor formation

* From The Lankenau Hospital Research Institute Philadelphia Pa

We may begin by repeating the well known but nevertheless remarkable fact that given the proper environment the fertilized ovum of any species will develop into an end product closely resembling its parents Furthermore it may be prophesied that given thousands of developing embryos of any one species under the same environmental conditions all of them will approach quite closely the average at any one time (except for occasional mutations)

Even in organisms which never stop growing *i e* never reach adult size so to speak—and the majority (in point of number) never stop growing—growth continues differentially in an appointed manner Thus a lobster of 25 pounds weight is built proportionately like a lobster of 5 pounds weight In those that do reach and maintain an adult size such as humans what growth occurs then is usually of local parts or systems and is in response to the needs of maintaining the organism as a whole against physiological needs wear and tear injuries etc

It is obvious that there is *order* in development in any and all stages Without entering further into a discussion of this phase it may be stated that these considerations can be built into an organismal philosophy for *Nature* in its entirety recognizing among other things that no organism or entity is merely a sum of its parts *From which it follows that no matter how finely the* parts of an organism are analyzed a complete picture cannot be obtained without a synthesis of all the parts and then of their interworkings into a whole The pathological appears when parts do not fit into the *whole* and it is just such a phenomenon which appears in tumor formation as far as we are able to see at present

The means by which this occurs is by distortion of at least two

tiplication of cells Differentiation is a broad term meaning numerous things at the present moment it means those changes within a cell which turn it into the more specific from the more general Later in discussing a special phase the term will be restricted and redefined Organization means the harmonious cooperative development of cells of various differentiations so that they can function into the frame of a whole Obviously the factors which determine differentiation and organization come from parents that is cells differentiate and organize true to their lineage whenever they proliferate

The cells of all tumors proliferate but they differentiate poorly and never organize as do normal cells Since neoplastic cells with their disorderly differentiation and organization often grow side by side in the very same environment with cells which exhibit

these properties normally, it would seem that the potencies of differentiation and organization are at fault within neoplastic cells

To turn to another phase, it is almost certain that when an individual cell reaches a certain point in its differentiation it loses the power of multiplication The term "differentiation is now *defined as follows Differentiation is the result of that series of* changes occurring within the protoplasm of a cell which brings it to the point where it is able to perform its function as a member of an adult organism

If, then the statement is true that fully differentiated cells in the sense stated above t differ entiation and with it of cell *division From this it* tious or interrupted cell multiplication takes place there must be present spare parts so to speak, from which the new multiplication can occur, or that cells in any given organ or part which retain the power of multiplication for whatever reason (physiological increase in number, repair regeneration etc) are not fully differentiated *

It is needless to say that this is an extraordinarily difficult state-*ment to prove if for no other reason than that accurate quantitative* measurements of degrees of differentiation of cells are still to be made But from the general finding that it is among anatomically

cells can divide At any rate the first step in investigating this

Inherent in this question is also that of dedifferentiation

seems unlikely It is far mo e p obab e differentiates the cells in the dedifferentiated tissue are not those that were previously present, but are new cells which have either failed to differentiate or have *differentiated in another direction*

This latter thought introduces considerations of cell potency as of fundamental importance We say that the fertilized ovum is of the adult organism are another of the potencies is expressed the number left possible of expression is diminished, but probably never below 2

* Carried to its logical conclusion this suggests that evolution from the general to the special has not ceased But who will say that evolution is completed?

As a specific instance, when the cells in the outer layer of the skin are shed, and their place is taken by new cells supplied from the basal layer, are these newly formed basal layer cells capable of turning into only an epithelium similar to the one shed, or have these basal layer cells several potencies? The question is answered thus far in one direction namely, that several potencies are present and which is expressed is determined by the environment in the broad sense of this term, so as to include extraneous factors and the influence of surrounding cells and tissues As an example of this idea, Wolbach and Howe s experiments may be cited[4] In animals fed on diets deficient in vitamin A, the cylindrical epithelium of the trachea and other regions is replaced by stratified squamous epithelium, this in turn to be replaced by the normal lining when vitamin A is again supplied in the food A similar phenomenon is observed in the restoration of normal expression of cell potencies in rickets Furthermore regeneration as exemplified in the regrowth of claws in crabs and other animals etc , also brings out the fact that protoplasm has more potencies than are usually expressed in a normal individual Even in mosaic ova some degree of adjustment is possible, while in developing regulatory ova as many as 8 larvae can be developed from 1 egg by suitably severing the cells as they are produced[5]

The large question in neoplasm is not how many potencies are present in the division-capable cell, or cells from which the tumor arises and continues to grow but what is their quality for this determines whether or not they are to be a neoplasm or will differentiate and organize normally Smaller questions, mainly in morphology, concern themselves with the number of potencies, for the more that are present the more

surrounding tissues Furthermore, since differentiation and espe-

adult organism in which they happen to occur, the rate of growth of early embryos being tremendously faster than that of older ones, it would seem that the rate of proliferation of neoplastic cells should be in direct proportion to the degree of disturbance of

of great practical importance[6]

Finally genetics supplies us with the fact that the incidence of tumors can be increased by inbreeding even though the details of how this increase in susceptibility is transmitted are still in process of study [7]

To summarize in relation to renal neoplasms It need not surprise us

1 That the less their cells are differentiated and organized the more rapidly they grow

2 That with the kidney developing embryologically from nests of cells with potencies for producing many structures tumors should occur in the kidney anatomically resembling structures in the neighborhood *e g* hypernephromas

3 That attempts at regeneration should often fail in their purpose for to regenerate an entire functioning renal unit requires that vessels glomeruli and all the tubule parts should be reconstructed and then joined to an outlet into the pelvis of the ureter

4 That nodules called adenomas should be relatively common for in many cases they are probably caused by attempts at regeneration

5 That many tumors should be composed of embryonal cells growing in masses utterly unlike any normal structure This brings the opportunity of again condemning the word embryonal in relation to the cells of a neoplasm Embryonal cells are cells with normal potencies not yet expressed neoplastic cells have altered potencies When cells with normal potencies are prevented by the environment from properly expressing them the result is an anomaly or an Albrecht hamartoma

6 That the metastases of many renal tumors should be rapid and widespread For metastasis occurs because the brakes to proliferation *viz* differentiation and organization are disturbed and the more complete the disturbance the more rapid the proliferation *i e* brake relaxed on their expression for totipotentiality (?) or potencies altered (?) Many renal tumors are composed of poorly differentiated and utterly unorganized cells

7 That some renal tumors show adeno formation others papillary structures others squamous cell like arrangements and even especially from the pelvis of the ureter cornifying squamous cell growths That is to say metaplasia is the expression on the part of a cell of a potency other than the normal for the part

8 That more renal tumors may develop in some human families than in others even though the details are in controversy

It remains to tabulate the main forms of renal tumors referring the reader to the standard texts for various details

GENERAL CHARACTERISTICS OF MALIGNANT RENAL TUMORS

and even into the heart itself Occasionally the renal vein is completely occluded whereupon infarction of the entire mass occurs Metastases are often early and widespread because of this tendency to invade vessels Skeletal metastases may be the first symptoms In a case observed in a boy aged fifteen years a nodule was removed from the upper right eyelid by an ophthalmologist Pathological diagnosis was hypernephroma whereupon examination of the child s abdomen disclosed a mass in the right renal region which subsequently proved to be hypernephroma Invasion into the ureter obstructs this passageway with subsequent hydronephrosis pyonephrosis or complete atrophy of what secreting units remain Invasion downward and appearance at the ureteral orifice in the *bladder is also not uncommon In a recent case observed a papil* lary carcinoma was found in a removed kidney Two years later urinary complaints led to cystoscopy whereupon a fungoid mass was seen protruding through the ureteral orifice on the side from which the kidney had been removed This was extirpated and the structures of this and of the original kidney tumor were identical

CLINICAL COMMENTS

Large tumors of the right kidney push the ascending colon upward and to the left Those of the left kidney push the descending colon upward so that it passes between the tumor and the anterior abdominal wall

In addition to such first clinical symptoms as mentioned above in the form of metastases hematuria occurs in upward of 60 per cent of cases Local pain and a palpable tumor are next in order

THE TUMORS

Benign tumors of many types have been described The com monest are the so-called adenomas and fibromas both of which are without clinical significance and are regarded by many as stated above as being the results of abortive attempts at regeneration

Since in the development of the kidney the potencies of some cells include that of the production of smooth muscle as it occurs under the capsule fibroleiomyomas also occur A curious combi nation of multiple small tumors containing fat fibrous tissue

smooth muscle and vessels in the kidney with rhabdomyomas of the heart and tuberous sclerosis is described

The characteristic malignant tumor of the child consists of rapidly growing bulky highly malignant structures containing both epithelial and connective-tissue elements hence its name adeno-sarcoma The connective tissue takes various forms such as the ordinary fibrillar type myxomatous type myomatous type while the glandular elements take on bizarre shapes and are of different sizes Their origin is in dispute but since some have produced metastases purely epithelial in nature others purely sarcomatous and still others containing both elements it may be stated from the point of view of cellular biology that the epithelium occasionally leads the procession and is followed as an attempt at organization by the connective tissue in others both types develop independently of each other but together in a heterogenous mass It has been stated that they arise from very early undifferentiated tissue such as the first mesodermic cells by others that they are derived from cells of the embryonal kidney and thus they are spoken of as malignant nephromas But in considering these ideas the following two possibilities may be put in the form of a question—do or do not malignant tumors arise in the following two circumstances (1) Mere mechanical displacement of undifferentiated cells and (2) the bringing together in abnormal juxtaposition of cells with two different potencies namely for producing connective tissue and for producing epithelium *i e* is or is not abnormal mingling alone a cause of malignancy?

The author believes at present that either of the two above-stated occurrences leads to the formation of an anomaly in the sense of hamartoma and not a malignant tumor That is to say if the internal potencies of the cells whatever they may be are not changed some kind of organization however poor will be accom

expressed are changed not in degree but in kind from those of their normal neighbors which produce the kidney and other sur rounding structures

The characteristic tumor of the adult of middle or advanced age is the hypernephroma For convenience they are divided into typical and atypical those words referring to (1) arrangement of the cells within the tumor many specimens of which show an attempt at layers as in the cortex of the adrenal and (2) atypical in the sense that no arrangement at all is apparent The latter also can be distinguished by its invasive tendencies into the sur roundings and into vessels

Thus the author has seen typical hypernephromas removed on the diagnosis of renal tumor from the symptom unilateral hematuria They were encapsulated sulphur yellow rounded or angular with architecturally well arranged cells The picture has been interpreted as relatively benign as contrasted with others of atypical characteristics

Doubts are often expressed as to their adrenal like origin Indeed doubts are again and again expressed as to their specificity some calling them a particular kind of carcinoma [9] The author believes they must be placed in a class by themselves both on anatomical grounds and because of their invasive behavior Whether it is necessary for their origin to have special cells present with potencies to produce adrenal like structures or whether ordinary kidney cells retain within themselves hidden potencies for producing them remains to be solved In either case what potencies are present are qualitatively different than those of the normal cells As far as their physiology is concerned they at least do not produce the changes in secondary sex characteristics such as are seen in true adrenal tumors The cells of hypernephromas are often highly vacuolated and contain fat globules and often much glycogen It would be interesting to know their carbohydrate metabolism in Warburg s sense It would also be interesting to correlate their well marked tendency to invade vessels with some peculiarity of permeability of renal vessels or susceptibility to enzymes or some peculiarity in the enzymes of the tumor cells themselves etc

Carcinomas of the kidney take on an a leno architecture or a papilliferous architecture or no architecture at all By the latter is meant that nests and groups of cells invade in all directions The pelvis of the ureter gives rise to papilliferous carcinomas with cells of the transitional type In addition non-cornifying and cornifying squamous-cell carcinomas are not uncommon The latter occur particularly when stones are present While stones but more especially incrustations are not uncommon in carcinomas involving the pelvis the question of whether they are primary or *secondary is an individual one clinical symptoms in certain cases* seem sufficient evidence that stones were present for some years before carcinoma developed Their relationship is of course the old one of chronic irritation plus predisposition The author has

expressed

PROGNOSIS OF MALIGNANT RENAL TUMORS

sion downward by direct spread and through the lymphatics of the ureter is common, no surgical removal is complete without this structure being also removed

The author has had no experience with radiation of these tumors except as a palliation in extensive deposits

REFERENCES

1 EWING, J 1922 Neoplastic Diseases Philadelphia, W B Saunders Company, p 738 KAUFMANN, E 1929 Pathology, translated by S P Reimann, Philadelphia, P Blakiston s Son & Co , 2, 1387 and onward

2 SHARP I W 1926 Introduction to Cytology, New York, McGraw Hill p 73 and onward

[illegible] Mutationstheorie der [illegible] CURTIS, M R DUNNING W [illegible] y due to a process analogous to [illegible] EDITORIAL 1934 J Am Med Assn , 102 [illegible]

4 WOLBACH, S B , AND HOWE, P R 1933 Epithelial repair in recovery from vitamin A deficiency, J Exp Med , 57 511–521

5 See discussion of potency in DURKEN B 1932 Experimental Analysis of Development, translated by H G and A M Newth, New York, W W Norton & Co p 82 and onward

6 REIMANN S P 1929 The issue at stake in the grading of tumors, Arch Path , 8, 803–815

7 EDITORIAL 1933 Cancer and genetic constitution Am J Cancer, 19 638–644

8 CRAWFORD B L 1932 *The classification of tumors of the kidney*, with especial reference to malignant tumors in adults, Am J Path , 8, 615–616 See discussion following

CHAPTER XXVI

KIDNEY TROUBLE IN ACUTE LUPUS ERYTHEMATOSUS

By ISIDORE SNAPPER M D

Symptoms —The skin disease named lupus erythematosus or as Unna called it ulerythema centrifugum is widely known This affection is characterized by red infiltrated patches situated in the

heal gradually beginning from the center and leaving an atrophic cicatrization The lesions are usually localized on the face and scalp however the hands and mucosæ may also be affected The disease lasts for years and usually undergoes exacerbations in winter and improvement in summer

The most typical feature is the *localization on the face* There the lesion spreads symmetrically over the cheeks and nose tip whereby the exanthema can be compared to a butterfly or a bat and explains why the name of vespertilio is so often used The scabs and scales of this affection have a characteristic quality Removing a scale which usually is not very easily done one may observe that the scale has been fixed at its base in the skin with little thorns after removal wide and patent follicles become visible

The name lupus erythematosus is hardly justified because this condition certainly has nothing to do with lupus vulgaris or other tuberculous lesions No tubercles nor tubercle bacilli are found in the infiltrated skin of the lupus erythematosus Often tuberculin reactions are negative

Lupus erythematosus seems to be purely a skin disease about which until now internists have had nothing to say There is however a variety of lupus erythematosus in which complications of the internal organs develop frequently *i e* acute lupus erythematosus It may happen that in a patient with ordinary lupus erythematosus *an acute generalization of the erythema suddenly develops* Sometimes the disease is acute from the onset and starts as an acute exanthema This last variety is called lupus erythematosus acutus disseminatus[1] Acute lupus erythematosus displays the following symptoms

(*a*) *Skin symptoms* In the really acute cases red patches appear on the face and soon flow together Sometimes a vespertilio form appears Very often crusts are formed so that this affection makes the impression of an eczema impetiginosum or of erysipelas bullosum explaining why these patients are often sent to the erysipelas wards Afterwards patches appear on the back of the hands and feet sometimes on the trunk Especially on the hands these patches may show characteristic properties of the lupus erythematosus lesion because of the atrophic centrum The lupus erythematosus often spreads to the gingiva causing an ulcerous gingivitis *without typical appearance It must be maintained that the* diagnosis of acute lupus erythematosus may be difficult because non typical lesions vesicles and hemorrhagic blisters often develop on the skin

(*b*) *High fever*

(*c*) *Kidney symptoms*

(*d*) *Often bronchitis and pneumonia*

(*e*) *Sometimes endocarditis or peritonitis*

(*f*) *Swelling of glands in axilla or (and) neck*

Incidence This disease is most frequent in women In 1923 only 3 cases of acute lupus erythematosus in males were reported

Etiology —So far as the etiology is concerned different opinions prevail It has been connected with (*a*) tuberculosis (*b*) streptococcus sepsis (*c*) special granulomatous degeneration of the lymph glands

— ' n the standpoint of
with acute inflam
he kidneys Here

the author wishes to point out the frequent association with inflammation and degeneration of the kidney Two cases he observed personally showed an insufficiency of the kidney as the outstanding symptom This caused him to look up the record of 4 other cases which had also been observed in Amsterdam In these 4 cases kidney symptoms had also been observed

Case Histories Case 1 —K Male Admitted June 1 1929 The patient had been under the care of a skin specialist for three weeks for

s a typ cal brownish exanthema

ilvarsan glycerin the general
ylate injections resulted in no
) 9 No autopsy
years Entered the hospital
he last six months For three

months she had had high fever and skin affection which started at the tip of the nose and afterwards appeared on the hands fingers and toes

On admission she had butterfly exanthema on the face There were scabs on the tip of the nose finger tips and toes raw underneath, evidently open blisters Her lips were swollen

There was a fine tremor in the muscles of the face, tremor and clonic contractions were present in the hands

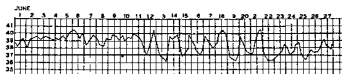


Fig 91 —Temperature record of Case 1

Urine Albumin 0 3 per cent many white blood cells some red blood cells, a few casts

Blood urea 30 mg per cent

[illegible] on the fingers and toes

[illegible] er cent Blood pressure,

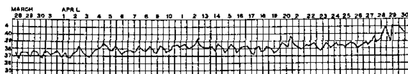


Fig 92 —Temperature record of Case 2

Case 3 —S H Female aged twenty years Admitted November 11, 1929 She had been healthy until five weeks previously At that time symptoms began with fever chills and headache After two weeks red [illegible]

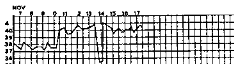


Fig 93 —Temperature record of Case 3

Urine Albumin +++ red blood cells +++ granular casts, +++

Blood pressure 105 60 For a few days before death, diarrhea Death, November 18 1929

Autopsy Bronchopneumonia left lower lobe Right lung small patches of bronchopneumonia Spleen enlarged, 215 gm , liver, 1600 gm ,

rash began on hands afterwards on face She had had fever for six weeks
At the time of admission she had scales on the scalp and red patches on *both arms and right knee* pneumonia of the lower lobe multiple abscesses on the trunk and thighs hemorrhagic stomatitis

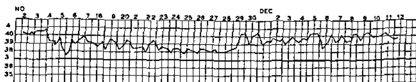


Fig 94 Temperature record of Case 4

Urine Albumin 2 per cent red blood cells + white blood cells + granular casts +
Death December 12 1929

300 gm Microscopic ... with hemorrhages there were some conglomerations of mononuclear cells no acute or chronic glomerulitis no proliferations of interstitial tissue tubules show autolysis cloudy swelling of the cells of the tubuli contorti still visible

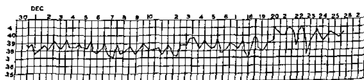


Fig 95 —Temperature record of Case 5

Case 5 —D *Male aged eighteen years* Admitted November 30 1925 The patient had had rheumatism for five months for four months he had had tenderness and swelling of all joints and rash on the upper lip and chin The rash started on the upper lip and spread like a butterfly over cheeks nose and eye-brows
On admission, he also had red patches with central atrophy on the tips of the fingers and toes right and left pleurisy heart enlarged with presystolic murmur
Urine Albumin ++ red blood cells ++ white blood cells ++ hyaline and granular casts +++
Blood pressure 190/110

liver normal Kidneys macroscopic Kidneys are somewhat enlarged

g u l elu r tle and u cle blood may be seen in the tubules casts slight increase of the interstit um with edema

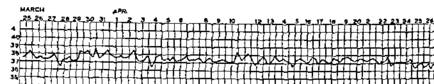


Fig 96

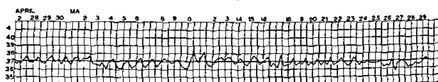


Fig 97

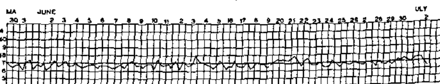


Fig 98

Figs 96 97 98 —Temperature records of Case 6

Treatment —All 6 cases died proving once more that in this condition therapy is of no avail However some of the published cases have survived Several authors therefore have advocated different treatments (*a*) Cacodylate injections intravenously (*b*) quinine injections (*c*) roentgen ray irradiation (*d*) blood transfusion In the author s patients therapeutic measures have had no beneficial effect

Kidney Lesions These 6 cases show that acute lupus erythematosus usually presents itself as a septic condition in which the typical lesion of the skin can be found No endocarditis was present in

or subacute
os 3 and 4

were not so severe as m ght have been expected con idering the symptoms during life In the 2 other cases which came to autopsy Nos 5 and 6 clear-cut kidney lesions were present

Evidently tuberculosis does not seem a probable cause for acute lupus erythematosus as in only 1 of the 4 autopsies recorded here were s gns of active tuberculosis found Swelling of glands was

present, but swelling of glands cannot be considered as a specific disease

The most remarkable case is the sixth patient in whom the symptoms of nephritis were discovered before the skin symptoms started The patient entered the hospital because she suffered from nephritis and from fever, probably caused by bronchopneumonia In the hospital the skin symptoms developed At first they made a non-specific impression, and only in the long run could the dermatologists be convinced that acute lupus erythematosus was really present Remarkably enough, the fever subsided one and a half to two months after the skin lesion developed and the patient maintained normal temperatures for two months, although she had typical symptoms of acute lupus erythematosus She died of renal insufficiency

These 6 cases show again that there must be an intimate connection between acute lupus erythematosus and nephritis however, the real reason why acute lupus erythematosus is so often complicated by nephritis remains just as mysterious as all the other complications of this remarkable disease Perhaps the solution of this problem can be furthered if all cases of acute lupus erythematosus be considered as patients with a general disease Functional examination of the kidneys of these patients even though they do *not show salient symptoms of nephritis will certainly give important* results

TABLE 51 —SUMMARY OF SIX CASES OF LUPUS ERYTHEMATOSUS

	Urine				Blood urea mg %	Blood pressure mm Hg	Blood culture	Autopsy
	Alb	R B C	W B C	Casts				
♂ K	0 5%	++	++	++	2 5	140 (sys)	Neg	
♀ D B	0 2 1 1%	+	++	++	80	160/90	Neg	
♀ Tr	0 05 0 2%	+	+	+++	?		Neg	Parenchym degeneration tubuli cont I
♀ H	+++	+++	++	++	100	10 /60	Neg	Glomerulitis acuta?
♂ D	+++	+++	+++	+++	?	160 100	Pneumococcus 2 days before death	Glomerulitis haemorrh nephritis parenchymatosa
♀ J D	0 13 1 2%	+++	++	+	150	10 /170 85/110	Neg	Glomerulonephr productiva chron

REFERENCES

1 GAWALOVSKY, K 1929 Lupus erythematosus acutus, Acta dermat venereol, 10, 1–30

2 GOECKERMAN W H 1923 Lupus erythematosus as a systemic disease, J Am Med Assn, 80 542–547

3 VAN DER VALK, J W 1922 Ueber Lupus erythematodes acutus d emblée Acta dermat venereol, 3 63 71

See also

LIBMAN E AND SACKS, B 1924 A hitherto undescribed form of valvular and mural endocarditis, Arch Int Med, 33 701–737

PART IV

ALBUMINURIA AND EDEMA

CHAPTER XXVII

MINIMAL ALBUMINURIA AND TESTS FOR ALBUMIN IN THE URINE

By THOMAS B MAGATH PH D M D

General Considerations Tests *for the presence of albumin in the* urine are given in all laboratory manuals Compared with most tests of every-day use these give the impression of extreme simplicity Yet they may be discussed with advantage Practically the tests for albumin are the most direct tests based upon the visual demonstration of the precipitated protein while theoretically the two problems involved the denaturation and the solubility of proteins constitute intriguing chapters of colloidal chemistry It is frequently said that no other single laboratory procedure is of greater clinical value than the albumin test It is important to realize that with the organization under which medicine is practised today especially in the United States most urines are analyzed by technical assistants and not by the responsible *physician himself The isoelectric point of the proteins is* nothing but Arabic to most technicians and it would be a mistake to expect these faithful helpers to know that when the urine is [illegible]

margin of safety in the performance and interpretation of the tests for urinary proteins On a moment s reflection nobody will gainsay the statement that there is a greater assurance of a correct result of a blood sugar determination than of a heat test or Heller s test In the more complicated blood sugar determination every step is precisely described and the personal equation almost eliminated Not so in the older and dominating tests for albumin *The answer as to reliability here to be given* consists of a comparison of several tests

From a physiological and clinical viewpoint the problems are two namely the degree of sensitiveness and *the pathological* significance of minute amounts The answer to the latter question is of importance in the field of life insur[illegible] recovery from acute nephritis and in essential hype[illegible] The answer partly depends upon the sensitiveness of the [illegible]

The sensitiveness of the heat and acetic acid test and of Heller's test is not considered as excessive. It is particularly true that the albumin normally present in the urine for reasons at best partly understood does not render Heller's test positive. Most of our knowledge of the albumin present in normal urine rests upon the work of Morner.[13] By means of a laborious technique starting with dialysis of 1 liter samples this accurate investigator demonstrated the presence of albumin in the urines from 20 men and 22 women all with negative Heller's test. In the urines from 10 men Morner determined the amounts quantitatively, obtaining values ranging from 2.5 to 8.9 mg. of protein per 100 cc. Morner considered this protein to be serum albumin. As to the physiological significance of this albumin knowledge is still wanting. One is reminded of Benedict's glucuresis and the name *albumuresis* might not be inappropriate. In regard to glucosuria we know that when it occurs the sugar at once appears in quantities entirely outside of the range of normal glucuresis. Whether the same holds true for albuminuria and albumuresis is not known.

The question arises whether by the use of the more sensitive tests for albumin, particularly the use of sulphosalicylic acid, one has

Heller's test and on urines the sensitiveness is again three times greater. The conversion of the sulphosalicylic acid test into a quantitative or semiquantitative method might have furthered our knowledge as to the significance of minute amounts of albumin but the reports have not yet been made available. That the danger of introducing too sensitive a test for routine examination has been realized might be induced from the fact that Folin advised a procedure for the sulphosalicylic acid test ten to fifteen times less sensitive than what could have been obtained.

THE MOST COMMON TESTS FOR ALBUMIN

Before making tests for albumin any urine that is not clear must be filtered or centrifuged. For routine work by technicians all specimens had best be subjected to filtration.

The Heat Test.—The oldest test used before the days of Bright consisted in heating the urine in a metal spoon, the protein, if present, coagulating at about 58° C. and giving a cloudy precipitate. Since most urines are acid it is often unnecessary to add acid to produce flocculation, but for alkaline urines proper acidification is necessary.

Heat and Acid (Acetic or Nitric) Test.—When acetic acid is used one must avoid adding an excess. The common practice is to place about 10 cc. of urine in a test tube, heat the top layer over the flame

and add 3 drops of 10 per cent solution of acetic acid By slightly

but if it increases it is due to albumin If the urine is markedly alkaline or rather possesses a high acid-combining capacity as sometimes in cases of nephrosis the prescribed drops of acetic acid may not suffice neutralization becomes necessary before the heating and the addition of the acetic acid Very low salt content of the urine likewise makes flocculation difficult

The test is always accurately done if Sørensen s acetate buffer

To about 10 cc urine in a test tube 1 cc of the reagent is added The whole solution is heated over the flame and boiled for one half minute With fair amount of albumin flocculation occurs directly if less than 0 05 to 0 1 per cent is present an opalescence first develops changing after a few minutes to a fine flocculation On the second boiling the flocculation occurs at once Even with this procedure an alkaline urine has first to be rendered neutral

This test is well discussed by Bang[1] The works of Sørensen[17 18] *are of fundamental importance for its theory*

This test is to be preferred to the use of heat and nitric acid If nitric acid is used care must be taken not to add too small an amount else precipitation will not take place It is necessary to add 1 or 2

of urine

urine has

addition of the acid

A number of substances may interfere in this test nucleoalbumin mucin albumoses secondary proteoses and resinous acids excreted after the intake of copaiba cubeb and benzoin all give some cloudiness The behavior of Bence-Jones protein is discussed in Chapter XXXI

Heller s Test —Although Heller mixed urine and nitric acid the test has survived as a *ring or contact test* * The urine is either

* In the paper by Heller
ser Fluss g
44) he dis-
fers to the
chon durch

layered on the top of the acid by letting it gently trickle out of a pipette along the wall of the test tube or the acid is layered under neath which is the way usually given in the older literature A precise method is to introduce the urine into the nitric acid by

The test can be read immediately if a ring or rather a meniscus of protein shows up or after two minutes if the ring is slow in com ing Folin states that it might be read after ten minutes and Morner who did important work on the test read it after fifteen minutes If the danger in the heat test is that protein present fails to flocculate the danger in Heller s test is that one of the non-specific rings be mistaken for albumin In concentrated urines rich in ure
the compo
gl stening 1
diluted with 1 or 2 volumes of water The remaining rings form a little above the contact zone One slightly grayish might form in concentrated urines from precipitation of uric acid as the nitric acid diffuses upward This too does not occur if the urine is diluted The other ring is white diffuse in outline and commonly found According to Morner it is due to condroitin sulphuric acid and usually becomes more distinct when the urine is diluted Bence-Jones proteins give a typical albumin ring

The following two tests are based on the ones just described

Purdy s Test —To a test tube two thirds full of urine is added about one-sixth of its volume of saturated solution of sodium chloride and 5 to 10 drops 50 per cent acetic acid After boiling

stood only practically The use of Sørensen s buffer solution is more rational

Robert s Test This test which is applied by the ring or contact method has for its reagent a mixture of nitric acid 1 part and
lphate o parts It is
Bence-Jones protein

In this test the effect of strong mineral acid on proteins is over shadowed by the effect of concentrated sulphate solutions on protein solub lity

and add 3 drops of 10 per cent solution of acetic acid By slightly

of acid the precipitate was due to calcium ammonium phosphate but if it increases it is due to albumin *If the urine is markedly* alkaline or rather possesses a high acid combining capacity as sometimes in cases of nephrosis the prescribed drops of acetic acid may not suffice neutralization becomes necessary before the heating and the addition of the acetic acid Very low salt content of the urine likewise makes flocculation difficult

The test is always accurately done if Sørensen s acetate buffer solution is used This reagent which keeps indefinitely is made as follows 56 5 cc glacial acetic acid and 188 gm sodium acetate dissolved and made up to 1 liter The test is carried out as follows To about 10 cc urine in a test tube 1 cc of the reagent is added *The whole solution is heated over the flame and boiled for one* half minute With fair amount of albumin flocculation occurs directly if less than 0 05 to 0 1 per cent is present an opalescence first develops changing after a few minutes to a fine flocculation On the second boiling the flocculation occurs at once Even with this procedure an alkaline urine has first to be rendered neutral

This test is well discussed by Bang[1] The works of Sørensen[17 18] are of fundamental importance for its theory

This test is to be preferred to the use of heat and nitric acid If nitric acid is used care must be taken not to add too small an amount else precipitation will not take place It is necessary to *add* 1 ... meter of urir ... the urine ... the addition of the acid

A number of substances may *interfere in this test nucleoalbumin* mucin albumoses secondary proteoses and resinous acids excreted after the intake of copaiba cubeb and benzoin all give some cloudiness The behavior of Bence-Jones protein is discussed in Chapter XXXI

Heller s Test —Although Heller mixed urine and nitric acid the test has survived as a ring or contact test * The urine is either

* ... In ... he paper by Heller ... Flüssig ... he d s- ... s to the ... n durch ... of

Secondary proteoses fall out of solution and cause opalescence when the tube cools

A final concentration of the sulphosalicylic acid of 2 per cent is sufficient for complete precipitation of protein For serial determinations Folin advised the use of 1 cc of urine in a long test-tube graduated at 25 cc, a 2 per cent solution of sulphosalicylic acid to be added to the 25-cc mark Through this dilution the test becomes specific and of reasonable degree of sensitiveness The standards for comparison devised by Folin corresponded to 0 03 0 05 0 1, 0 2 and 0 3 per cent albumin That the lowest standard corresponded to as high a concentration as 0 03 per cent albumin was significant the method was devised for use in examinations for life insurance After several years use of this procedure Kingsbury[10] somewhat altered it and also introduced permanent artificial standards the basis for them being formazin suspended in gelatin Kingsbury s alteration represented a swing toward a more sensitive test He increased the urine to one fourth of the final volume using 2 5 cc of urine and filling up to a 10-cc mark with 3 per cent sulphosalicylic acid Kingsbury s standards corresponded to a protein concentration in the amount of urine used of 0 01 0 02 0 03 0 04 and 0 05 per cent

All methods so far described have required a minimal amount of laboratory equipment

The Scopometer Method — A more elaborate quantitative method than comparisons with standard tubes is available in Exton s junior scopometer an instrument for the measuring of turbidity and colors in routine work For turbidity measurements Exton finds it better than the ordinary nephelometer The phenomenon used in the scopometer is the disappearance of an image in the instrument The end point in the determination is the vanishing

of a standard target to vanish For adding density one uses a wedge The position of the wedge is read off on a scale The optical density for the different points of the wedge being known the density of the unknown is obtained and empirically converted into concentration of the unknown A detailed description of the use of this instrument for the determination of albumin in the urine does not seem to have been published The method must require that urines that are moderately rich in albumin be diluted in order to obtain a sufficiently stable dispersion of the precipitated protein For minute amounts in which one chiefly determines the opacity of the wedge slight variations in the degree of dispersion might greatly affect the reliability

Tests With Picric Acid *Stewart s Qualitative Test* —The reagent for Stewart s test consists of picric acid (wet) 10 gm , magnesium sulphate 400 gm citric acid 20 gm , and distilled water 1500 cc The test is a ring test carried out in the usual manner Stewart claimed that this test was more highly specific and more readily applied than the test by heat and acid

Esbach s Quantitative Method —Esbach s reagent consists of picric acid 1 gm citric acid 2 gm and distilled water to make 100 cc The results obtainable with this well known sedimentation method are of no clinical value in the medicine of today To obtain the quantitative estimates now desirable the method is too inaccurate

The following reagents trichloracetic and sulphosalicylic acid are excellent protein precipitants They are applied either as contact tests or as turbidity tests For recognition of minimal amounts the turbidity tests are particularly elegant the slightest amount of turbidity causing an opalescence which is easily distinguished from a clear control if one looks through the tube longitudinally or in transmitted light The turbidity tests lend themselves to semiquantitative determinations by comparison with standards of known concentrations

A trichloracetic acid concentration of 2 5 per cent in the final solution is sufficient for complete precipitation if the albumin is at all abundant For minute amounts the test may be arranged so that a final concentration of 10 per cent acid is obtained For a ring test a reagent has been used consisting of a saturated solution of trichloracetic acid to which magnesium sulphate has been added to saturation

Sulphosalicylic acid was applied as a protein precipitant by Roch [15] in 1889 and by MacWilliam [14] in 1891 who in arranging his test even made use of the opalescence produced by minute amounts of protein The acid has been used in turbidity methods by Kober[11] and by Folin and Denis [7] later by Folin and Benedict [5] by Exton[2,3,4] and by Kingsbury [10]

In 20 per cent aqueous solution sulphosalicylic acid is used in a ring or contact test Urates and resins are not precipitated Under the name of Exton s test the acid is used as follows 200 gm of sodium sulphate are dissolved in about 750 cc of water with the aid of heat The solution is cooled to about 35° C and 50 gm of sulphosalicylic acid are added dilution with water is made to 1000 cc Equal parts of urine and reagent are added in a test tube and warmed gently Boiling is not necessary or desirable A white cloud shows the presence of protein and the result is read while the fluid is warm since proteoses cause cloudiness when the liquid cools The Bence-Jones protein causes a heavy precipitate resembling curdled milk which clears partially or wholly on boiling

dilutions the use of Sørensen's buffer proved somewhat better than the addition of acetic acid drop by drop the sensitiveness being 1 in 50 000 and 1 in 25 000 to 33 000 respectively On urines the sensitiveness rose to 1 in 200 000 without any difference between

TABLE 52 — SENSITIVENESS OF HELLER'S TEST ON DILUTE SERUM AND URINE

Protein content Per cent	Test read after min 2	5	1	30	Material
0 002 (1 in 50 000)	–	–	–		Diluted blood serum
0 003 (1 in 33 000)	–	–	?		
0 004 (1 in 25 000)	+	+	+		
0 005 (1 in 20 000)	+	+	+		
0 006 (1 in 17 000)					
0 007 (1 in 14 000)					
0 008 (1 in 12 500)			–	+	Normal urine enriched by serum
0 009 (1 in 11 000)	–	–		+	
0 010 (1 in 10 000)	–		+	+	
0 0125 (1 in 8 000)		+	+	+	
0 015 (1 in 6 700)	+	+	+	+	

TABLE 53 — SENSITIVENESS OF TESTS WITH HEAT AND ACETIC ACID SULPHOSALICYLIC AND TRICHLORACETIC ACID IN DILUTE SERUM AND URINE

Protein content Per cent	Diluted serum: Heat and acetic	Heat and Sørensen	Sulphosalicylic	Trichloracetic	Enriched urine: Heat and acetic	Heat and Sørensen	Sulphosalicylic	Trichloracetic
0 0001 (1 in 1 000 000)	–	–	–	?				?
0 00025 (1 in 400 000)	–	–	+	+	?	?	+	+
0 0005 (1 in 200 000)	–		+	+	+	+	+	+
0 00075 (1 in 150 000)	–	–	+	+	+	+	+	+
0 001 (1 in 100 000)	–	–	+	+	+	+	+	+
0 002 (1 in 50 000)	–	? +	+	+	+	+	+	+
0 003 (1 in 33 000)	?	+	+	+	+	+	+	+
0 004 (1 in 25 000)	+	+	+	+	+	+	+	+
0 005 (1 in 20 000)	+	+	+	+	+	+	+	+

SENSITIVENESS OF THE VARIOUS ALBUMIN TESTS

The sensitiveness of the different tests proves a complicated matter Concerning Heller s test Hammarsten[9] stated that an *amount of albumin of 0 002* per cent (*1 in 50 000*) is easily detect able and in another mode of expression with negative Heller s test the urine contains less than 0 003 per cent (1 in 33 000) of albumin Morner[13] found the test less sensitive 0 008 per cent (1 in 12 500) Bang[1] saw in this relatively low sensitiveness an advantage and an assurance that the albumin content of normal urine is not picked up by this test Bang considers the heat and acetic test to be of about the same sensitiveness as Heller s test

Two or more questions are involved (1) What is the minimal amount of albumin detectable by the different tests? This is preferably tested on dilutions of serum with 0 9 per cent sodium chloride solution (2) Given these amounts of albumin present in urine how much if at all do other urinary constituents particu larly the colloids influence the sensitiveness? Different concen trations surely will have different effects Different diets too might influence the colloid content of the urine a point to which little attention has been given It might be recalled that Folin and Berglund[6] on feeding to a normal person a certain brand of dextrin recovered grams of
than maltose The influen
condroitin sulphuric acid c
(3) When investigating sensitiveness a different care is surely taken in creating favorable optical conditions for the detection of a faint reaction than in routine work particularly if urines are not examined in series but one by one How far does this reduce sensitiveness?

Inquiry into Heller s test (Table 52) shows a difference in sen sitiveness for the same amount of albumin depending on whether the albumin is in dilute sodium chloride solution or whether it is added to normal urine of medium specific gravity (negative for albumin according to the trichloracetic acid test) On serum the test was positive in dilution 1 in 25 000 the white ring appeared within two minutes and no increase in sensitiveness took place during fifteen minutes On urine the sensitiveness after two minutes was 1 in 6700 only with an increase of sensitivity to 1 in 12 500 after thirty minutes When the reading was made after five minutes the sensitiveness in *diluted serum was 7 5 mg per* 100 cc greater than in urine The role of the condroitin sulphuric acid and other protein precipitants normally present in urine which cause a reduction in sensitiveness will not be further con

M paper

(Table 53) is
On the serum

dilutions the use of Sørensen's buffer proved somewhat better than the addition of acetic acid drop by drop, the sensitiveness being 1 in 50,000 and 1 in 25,000 to 33,000, respectively. On urines the sensitiveness rose to 1 in 200,000, without any difference between

TABLE 52.—SENSITIVENESS OF HELLER'S TEST ON DILUTE SERUM AND URINE

Protein content Per cent	Test read after min. 2	5	15	30	Material
0.002 (1 in 50 000)	−	−	−		Diluted blood serum
0.003 (1 in 33 000)	−	−	?		
0.004 (1 in 25 000)	+	+	+		
0.005 (1 in 20 000)	+	+	+		
0.006 (1 in 17 000)					
0.007 (1 in 14 000)					
0.008 (1 in 12 500)			−	+	Normal urine enriched by serum
0.009 (1 in 11 000)	−	−	?	+	
0.010 (1 in 10 000)	−		+	+	
0.0125 (1 in 8 000)	−	+	+	+	
0.015 (1 in 6 700)	+	+	+	+	

TABLE 53.—SENSITIVENESS OF TESTS WITH HEAT AND ACETIC ACID, SULPHOSALICYLIC AND TRICHLORACETIC ACID IN DILUTE SERUM AND URINE

Protein content Per cent.	Dilute serum: Heat and acetic	Heat and Sørensen	Sulphosalicylic	Trichloracetic	Enriched urine: Heat and acetic	Heat and Sørensen	Sulphosalicylic	Trichloracetic
0.0001 (1 in 1 000 000)	−	−	−	?	−	−	−	?
0.00025 (1 in 400 000)	−	−	+	+	?	?	+	+
0.0005 (1 in 200 000)	−	−	+	+	+	+	+	+
0.00075 (1 in 150 000)	−	−	+	+	+	+	+	+
0.001 (1 in 100 000)	−	−	+	+	+	+	+	+
0.002 (1 in 50 000)	−	? +	+	+	+	+	+	+
0.003 (1 in 33 000)	?	+	+	+	+	+	+	+
0.004 (1 in 25 000)	+	+	+	+	+	+	+	+
0.005 (1 in 20 000)	+	+	+	+	+	+	+	+

negative and the others positive The heat and acetic acid test alone was positive in 8 instances Stewart s test alone was positive 3 times and the sulphosalicylic acid test alone once Thus these three tests give fairly consistent results

TABLE 55 COMPARISON OF VARIOUS TESTS ON 100 SPECIMENS OF URINE

Heat and acetic acid	Stewart	Sulphosalicylic acid	Instances of agreement per cent
Positive	*Positive*	*Positive*	*33*
Positive	Positive	Negative	6
Negative	Positive	Positive	5
Positive	Negative	Negative	8
Negative	Positive	Negative	3
Negative	Negative	Positive	1
Negative	Negative	Negative	44
		Total	100

Table 56 shows that the presence of leukocytes or pus is connected rather closely with the presence of protein and that when leukocytes were present all of the methods except Heller s test gave a high percentage of positive tests for protein Slightly more of the urines in which casts are present are positive by the heat and acetic acid test than by any other casts were found in 20 per cent of those positive for proteins by this method and in a slightly lower percentage by the other tests In 4 specimens of urine reported negative for albumin by all tests there were hyaline casts

TABLE 56 RELATION OF CASTS BLOOD AND PUS TO PROTEIN (100 SPECIMENS OF URINE)

	Positive protein specimens	Microscopic elements in specimens positive for protein per cent			
		Casts	Blood	Leukocytes or pus	Negative
Heat and acetic acid	48	20	19	94	2
Stewart	48	15	19	88	4
Sulphosalicylic acid	40	15	2[illegible]	92	[illegible]
Heller	7	14	43	86	
Positive protein*	56	25	16	96	4
Negative protein (all tests)	44	9		[illegible]8	63

* *Positive by some one test or by more than one*

SIGNIFICANCE OF MINUTE GRADES OF ALBUMINURIA

Evidence ... n the urine
of minute
nificance
this way This volume contains such contributions by

McKinlay and by Medes Sanford Conner Magath and Heck,[16] in 70 cases correlated the finding of albuminous urine with other significant data Definite renal lesion was present in 40 per cent while in 30 per cent any lesion remained uncertain In the absence

an Grade 1 by

ionable cases

In the group

of cases of renal disease albuminuria Grade 1 was recorded in 15, Grade 2 in 6 Grade 3 in 3 and Grade 4 in 2 The changed attitude of the life insurance companies toward albuminuria is significant Ogden[14] in 1915 made the statement Not many years ago insurance was refused any person whose urine contained albumin " At the same time he reported favorable ten years experiences from the insurance of a great number of individuals with slightest possible trace of albumin The knowledge derived from the quantitative determinations adopted by a number of insurance companies during the last decade forms the basis for the present mode of action Albuminuria in amounts up to 0 03 per cent does not prevent a person under thirty five years of age and with a negative previous history and otherwise normal findings from being accepted as a standard risk Even persons whose urine contains as much as 0 05 per cent of albumin might under some circumstances be rated as normal risks Thus the development that has taken place is this quantitative estimates carried out by methods

[illegible]

and in which albumin not detectable by Heller's test was demonstrated by one of the more sensitive methods the individuals were nephritics who otherwise had recovered except for the minimal amount of albumin in their urine and occasional red blood cells in the sediment or they had uncomplicated chronic hypertension In such cases the sensitive methods add valuable clinical information that otherwise is missed

REFERENCES

1 Bang I 1926 Lehrbuch der Harnanalyse 2 [illegible] ed München, J Bergmann

2 Exton W G 1923 A simple and rapid test for albumin and other urinary proteins, J Am Med Assn 80 529–530

3 [illegible] 1925 A simple and rapid quantitative test for albumin in urine J Lab and Clin Med 10 722–73[illegible]

4 [illegible] 1929 The [illegible] scopometer J Am Med Assn 92 708–712

5 Folin O and Benedict S R 1923 Application of quantitative chemical methods in examinations for life insurance The Metropolitan Press Also in Hawk's Practical Physiological Chemistry 8th ed Philadelphia Blakiston's Son & Co Appendix p 665, 1923

Wiesbaden

of certain protein

AND POST A L
and Clin Med
11 981–989

11 KOBER P A 1913 Nephelometry in the study of proteases II J Am Chem Soc 35 290–292

12 MACWILLIAMS J A 1891 *A new test for albumin and other proteids*, Brit Med J 1 837 840

13 MÖRNER K A H 1895 Untersuchungen uber die Proteinstoffe und die eiweissfallenden Substansen des normalen Menschenharns Skand Arch Physiol 6 332–437

14 OGDEN J B 1917 A study of 59 270 exposures of ordinary life
Proc Assn
132 172
eutische
K, F J
th Con
servation 30 20?–217

17 SØRENSEN S P L 1917 Studies on proteins Compt rend trav lab Carlsberg 12

18 ———— 1925 Proteins, lectures given in the United States of America in 1924 The Fleischmann Laboratories

19 STEWART U P 1918 A new contact test for albumin in urine J Am Med Assn 71 1050

CHAPTER XXVIII

ALBUMINURIA IN YOUNG MEN

By HAROLD S. DIEHL, M.A., M.D.

AND

CHAUNCEY A. McKINLAY, M.D.

Introduction.—The occurrence of albumin in the urine of sup-

of renal disease. Stirling[19] in 1887 noted the apparent relationship between posture and the occurrence of albumin in the urine of certain individuals. Teissier[20] in 1889 suggested the term orthostatic albuminuria. Since that time numerous studies of this condition have been made and opinions expressed as to its frequency and significance. In this chapter we are presenting the results of some studies of albuminuria in supposedly normal persons carried on in the Student Health Department of the University of Minnesota over a period of several years. The group which has been studied consists of 16,718 male students who entered the University of Minnesota between 1921 and 1928. Tests of the urine were performed as part of the entrance physical examinations. In test-

first examination. Over the seven-year period covered by this investigation the incidence of albuminuria varied considerably from year to year. This difference may have been due in part, at least, to different standards for the interpretation of the test. Attempts were made to prevent this, but inasmuch as the same technicians did not perform these tests throughout the entire period, the possibilities of different standards, particularly for minimal amounts, is possible. Ashburn[1] found a considerable variability in the incidence of albuminuria in West Point cadets in certain years and suggests the possibility of epidemics of albuminuria. Evidence supporting this suggestion is not convincing.

Comparisons of this incidence of albuminuria to that reported by others is somewhat unsatisfactory because investigators have used

different tests, the delicacy of which, as Dr Magath pointed out, varies widely Ashburn gives a report of 5855 routine urine examination on 2269 cadets Of this number, 7 per cent were reported as positive for albumin Parmenter[14] reports that over a period of four years 5 to 7 per cent of Harvard freshmen had albuminuria on a single examination Other writers[2,9,11,15] report incidences of 3 per cent to as high as 60 per cent This highest incidence was in children from two to six years of age, described by the authors, Calvin, Isaacs and Meyer,[3] as having had "poor care"

Results of Reexaminations —Over a period covering the later years of this study, 460 students who showed albumin on the first urine examination were reexamined One hundred and eleven of these had only one subsequent urine examination, but the others had from two to thirty specimens examined On the basis of these subsequent examinations the cases were classified as transient albuminuria, meaning albuminuria on only the first examination with later examinations negative, occasional albuminuria, frequent or persistent albuminuria and albuminuria with probably kidney damage As seen from Table 57 approximately two-thirds of the

TABLE 57 —RECLASSIFICATION OF ALBUMINURIA 460 CASES REEXAMINED

	Albuminurias per cent	Total (calculated) per cent
Transient albuminuria	68 3	3 6
Occasional albuminuria	13 0	0 7
Persistent albuminuria	12 0	0 6
Probable kidney disease	6 7	0 4

cases who showed albuminuria on the first examination had negative reports on subsequent tests while only 6 7 per cent had what seemed to be definite evidence of kidney damage Taking the results of these reexaminations as a basis and computing the inci-
... and kidney
transient
group
uminuria
ances or
general disease is still somewhat of a debatable subject Elwyn[5] states that in all types of albuminuria there is either a deficiency of oxygen supply or injury by a toxin and that in either case glomerular and capsular epithelium are damaged Russell[15] believes that orthostatic albuminuria is frequently caused by some form of

physical efficiency. Jehle,[10] in his exhaustive study, stressed the effect of exaggerated lordosis as a cause of albuminuria. However, the careful observations of Goetzky,[7] confirmed by many observers, indicated that as a cause marked lordosis is probably unimportant.

The significance of albuminuria to health has been shown by Dublin[4] and by Palmer.[13] Dublin computed the mortality rate over a period of approximately six years of 5000 persons who were rejected for life insurance because of albuminuria or albuminuria with casts. The mortality rate of persons in the age group fifteen to twenty-four years who showed only a faint trace of albumin with or without casts was no greater than expected, but the rate of persons in the same age group who showed a trace or large trace of albumin was from two to six times the expected. Palmer re-examined 35 Harvard graduates who had had albuminuria when examined as students approximately eight years before. In only 1 of these was there persistent albuminuria and in 1 more transient albuminuria at the time of reexamination. Although studies such as these suggest that small amounts of albumin in the urine unaccompanied by other evidences of kidney damage are without significance, it seems that further light on this condition may be obtained by a study of the physical and physiological characteristics of a group of persons who have albuminuria.

STATISTICAL STUDIES OF ALBUMINURIA IN YOUNG MEN

With this in mind three groups of students were compared as to age, height, weight, percentage, pulse-rate, blood pressure, histories of certain past diseases and the condition of the nose and throat. Group I is a control group composed of students with normal urinary findings, each one of which was examined just before or just after one of the students in the albuminuria group. Group II consists of students who had albuminuria on the entrance examination and Group III consists of students with probable kidney disease. The diagnosis of kidney disease in some of these cases was made by private physicians, but in the majority of the cases the diagnosis was made by members of the Health Service staff and was based upon urinary findings, chemical tests of the blood and tests of renal function, particularly the phenolsulphonephthalein test and the various water-concentration and dilution tests. While it is possible that a few students in the albuminuria group may have undiscovered evidence of kidney damage, the probability is that the number of these is very small because an effort was made to secure blood chemistry analyses and urinary function tests on all students who showed persistent albuminuria or any considerable number of casts, particularly granular, in the urine. It is possible too that some of the cases classified as nephritis, but upon which

of the control group and the albuminuria group are practically identical but the group with probable kidney disease has significantly higher pressures The percentage of the albuminuria group with blood-pressures of 130 mm or more is significantly greater than the percentage of the control group When one gets up to pressures of 140 mm or more the difference in percentages between the two groups is not significant This slight increase in the blood pressure of the albuminuria group probably is evidence of a nervous reaction

Diastolic Blood pressure The mean diastolic blood pressure of

higher level of pressure

Pulse pressure —Erlanger and Hooker[6] suggest that a diminution of pulse pressure is a possible cause of albuminuria and that the amount of albumin excreted varies inversely to the magnitude of the pulse-pressure As will be seen from Table 58 a comparison of the pulse pressures of these groups lends no support to this suggestion

Summary of Physical Findings These points brought out in the foregoing paragraphs are shown even more clearly in Table 59 where the differences between these findings in the three groups are given in columns 2 3 and 4 In columns 5 6 and 7 are tabulated the ratios of the differences to their probable errors As is known, when this ratio is 3 or greater the difference considered from a statistical point of view is held to be of significance

TABLE 59 DIFFERENCES BETWEEN VARIOUS GROUPS IN TABLE 58 TOGETHER WITH THE STATISTICAL SIGNIFICANCE OF THESE DIFFERENCES

	Difference			Ratio difference to its probable error		
	Group I minus Group II A	Group I minus Group III B	Group II minus Group III C	A	B	C
Age	*+0 1±0 1	1 [illegible]±0 5	1 80±0 5	4 3	2 4	3 5
Height weight percentage	*+2 38±0 [illegible]	+ 1 33±1 8	− 0 [illegible]±1 8	4 6	0 8	0 [illegible]
Per cent under 90	+[illegible] 12±2 10	+ 3 88±[illegible] 0	+ 0 [illegible]6± 0	0 1	0 6	0 5
Per cent over 90	+0 31±1 30	+ 1 73±4 5	+ 1 4 ±4 5	0 2	0 4	0 3
Pulse-rate	*+0 63±0 [illegible]	+ 0 [illegible]±1 7	+ 0 35±1 7	1 1	0 2	0 2
Per cent over 90	1 9[illegible] ±1 0	+ 4 42±5 4	+ 6 [illegible]±5 5	1 1	0 8	1 2
Systolic blood-pressure	* 0 14±0 58	10 [illegible]± 9	−10 [illegible]±2 9	0 3	3 7	3 7
Per cent over 130	7 80±2 10	−36 47±7 9	38 67±8 0	3 7	4 6	3 4
Per cent over [illegible]	2 [illegible]±[illegible] [illegible]	2[illegible] [illegible]± [illegible]	−2[illegible] [illegible]±7 9	[illegible] 6	3 2	2 9
Diastolic blood-pressure	*+0 [illegible]±0 47	6 67±[illegible] 9	− 7 43±2 9	1 7	2 3	2 5
Per cent over 8[illegible]	+1 [illegible]±1 10	−27 [illegible]±7 8	[illegible] 46±7 8	1 0	3 5	3 6
Per cent over 1[illegible]0	−0 [illegible]±0 41	16 [illegible] ±6 [illegible]	−16 11±6 2	0 7	2 6	2 6
Pulse pressure	0 [illegible]±0 3	4 1±1 1	− 3 [illegible]±1 1	1 3	1 0	[illegible]

* Mean

our own data are incomplete, might be questioned In spite of these possible inaccuracies, for purpose of comparison the groups are relatively satisfactory (Table 58)

TABLE 58 —RELATION OF ALBUMINURIA TO CERTAIN PHYSICAL AND PHYSIOLOGICAL DATA

	I Control group (no albuminuria) 480 cases	II Albuminuria (no demonstrable kidney damage) 455 cases	III Probable kidney disease 17 cases
Age	*19 59 ± 0 09	19 08 ± 0 08	20 88 ± 0 52
Height weight percentage	*96 15 ± 0 39	93 77 ± 0 35	94 62 ± 1 74
Per cent under 90	26 96 ± 1 40	26 84 ± 1 60	23 08 ± 6 90
Per cent over 110	9 42 ± 0 90	9 11 ± 0 90	7 69 ± 4 40
Pulse-rate	*82 63 ± 0 39	82 00 ± 0 44	82 35 ± 1 61
Per cent over 90	16 18 ± 1 10	18 10 ± 1 30	11 76 ± 5 30
Systolic blood pressure	*123 24 ± 0 40	123 38 ± 0 39	134 12 ± 2 58
Per cent 130 mm +	28 24 ± 1 40	36 04 ± 1 60	64 71 ± 7 80
Per cent 140 mm +	10 04 ± 0 90	12 31 ± 1 10	35 29 ± 7 80
Diastolic blood pressure	*74 21 ± 0 33	73 43 ± 0 33	80 88 ± 2 86
Per cent 90 mm +	7 97 ± 0 80	6 83 ± 0 80	35 29 ± 7 80
Per cent 100 mm +	1 26 ± 0 30	1 54 ± 0 30	17 65 ± 6 20
Pulse pressure	*49 03 ± 0 52	49 95 ± 0 51	53 24 ± 4 06

* Mean

Age —The average age of the control group is about one-half a year greater than that of the group with albuminuria, and the probable error is sufficiently small to make this difference seem significant Whether this difference in age is in line with the suggestion of Hess[8] and others that albuminuria is more frequent in children and adolescents than in older age groups or whether the difference is a mere chance will require further study The higher

whom had disabilities of nephritis

Height-weight Percentage —The height-weight percentage as here

percentage
han
per

cent of standard, however, is approximately the same in the two groups, indicating that the degree of the underweight in the albu-

u-
of
te
h

a makeup The mean pulse-rate of the albuminuria group is

ings only relatively accurate For comparative purposes however, they should serve satisfactorily Instead of attempting to list the various tonsil abnormalities which the nose and throat specialist noted these were all grouped together and the conditions tabulated as tonsils abnormal The frequency of this condition as shown in the table is practically the same for all groups Assuming

albuminuria group than in the control group Additional weight is added to this conclusion by the significantly smaller percentage of "normal tonsils" among the albuminuria group

TABLE 60 INQUIRY INTO THE RÔLE OF CERTAIN PREVIOUS OR PRESENT PATHOLOGICAL CONDITIONS

Incidence per cent of	I Control group no albuminuria 450 cases	II Albuminuria no demonstrable kidney damage 455 cases	III Probable kidney disease 17 cases	Difference Group I minus Group II	Probability of chance difference greater than or equal to actual difference
Scarlet fever	13.96 ± 1.1	1[illegible].38 ± 1.1	23.[illegible]3 ± 6.9	− 1.42 ± 1.60	1 in 4
[illegible]	5.21 ± 0.[illegible]	6.5[illegible] ± 0.8	11.76 ± 5.3	1.39 ± 1.10	1 in 5
Diphtheria	6.25 ± 0.7	6.37 ± 0.8		0.12 ± 1.10	1 in 2
Tonsillitis	3.96 ± 1.3	23.30 ± 1.3	17.65 ± 6.2	+ 0.66 ± 1.80	2 in 5
Frequent colds	16.01 ± 1.1	2[illegible].86 ± 1.3	23.41 ± 7.5	− 6.82 ± 1.70	1 in 287
Tonsils					
Absent	28.96 ± 1.4	38.24 ± 1.6	29.41 ± 7.5	− 9.[illegible]8 ± 2.10	1 in 1000
Normal	4[illegible].42 ± 1.6	33.41 ± 1.6	47.06 ± 8.[illegible]	+12.01 ± 2.30	1 in 5000
Abnormal	25.21 ± 1.3	27.47 ± 1.4	23.53 ± 6.1	− 2.26 ± 1.90	1 in 5
Chronic nasal discharge	0.42 ± 0.2	[illegible].42 ± 0.4		2.00 ± 0.45	1 in 1000

Chronic nasal discharge was the only condition tabulated in regard to the nose This was chosen because of its possible relation to sinus infection The incidence of this condition is not great in either group but it occurs significantly more frequently in the albuminuria group than in the control group

Discussion and Summary —The incidence of albuminuria in 16 748 supposedly healthy freshmen students at the University of Minnesota with an average age of approximately nineteen years was found to be 5 24 per cent The nitric acid ring test was used in making these examinations and results are based upon the examination of a single specimen Had multiple specimens from each patient been examined over a period of time or had more delicate tests been used the incidence would undoubtedly have appeared considerably greater Some writers[16 17] state that it is probable that all urine could be found in the urine of every person if a sufficient number of specimens were examined

Subsequent examinations were made of urine specimens of 160 students who had albumin on the first examination A reclassifica-

A general inspection of columns 2 3 and 4 of Table 59 reveals the fact that the differences between Groups I and II i e the normal subjects and those with albuminuria are in most cases relatively slight as compared with the differences between either of them and Group III the values in columns 3 and 4 being of approximately the same order This indicates that the normal subjects and those with albuminuria tend to resemble each other more closely

This is espe

The only

cally significant (column 5) aside from the age factor which has already been discussed are the height weight percentage and the significantly greater number who have systolic pressures over 130

Both Groups I and II are statistically different from Group III in regard to mean systolic blood pressure and the relatively lesser number having pressures over 130 and over 140 mm Hg The differences in the diastolic blood pressures on the other hand are

Group I or Group II Here again the differences in the ... pressures are not extreme as indicated by the lack of statistically significant difference in the percentage with pressures greater than 100 mm Hg

RELATION OF ALBUMINURIA TO OTHER DISEASES

Past Diseases and Frequent Infections —The frequency of the history of several diseases which seemed most likely to have some relationship to albumin in the urine were compared and these com parisons for the groups are displayed in Table 60 Scarlet fever shows increased incidence only in the group which has definite kid ney disease *The incidence of diphtheria is practically* the same in all groups but a history of rheumatism is given significantly more frequently by the group with probable kidney disease

Frequent Illnesses —On the history blanks students report as to the frequency with which they have various symptoms illnesses etc Attacks of ... nsidered to be related to kidney ... ximately equal fre quency by ... groups Frequent colds on the other hand show a significant relat onship to the occurrence of albuminuria

Condition of Nose and Throat As part of the entrance physical examination the nose and throat of each student is inspected by a nose and throat specialist and the report of the condition observed is recorded These examinations are hurriedly done and the find

10 JEHLE L 1914 D e Albuminurie kl n sche und exper mentelle Be tr ge zur Frage der orthostatisch lordotischen und der nephritischen Albuminur e
n c

s an l
and

Iosp

ne] 25 200 244
13 PALMER R S 1931 Funct onal albuminuria J Am Med Assn 96 1559–156?
14 PARMENTER, W C 1920 Observations on the s gnificance of f nctional albuminuria in young men at Harvard University Boston Med and S rg J 183 677–681
15 RUSSELL, J W 1925 The origin and s gnificance of postural (ortl o-

1 0 100
20 TEISSIER, J L 1899 Albuminurie de la station debout albuminurie orthostat q e Semaine méd 19 4.5–427
21 THORP E G AND WAKEFIELD E (1933 Orthostatic alb umin iria a comparison with other types of albuminuria Ann Int Med 6 1565–1578

tion made from the results of these later examinations showed that 68 per cent had only transient albuminuria 13 per cent occasional albuminuria 12 per cent frequent or persistent albuminuria and 7 per cent probably kidney disease

types however is indefinite and every examiner finds numerous cases which do not seem to fit into any of these categories

The etiology of this type of albuminuria in healthy persons is not clear The upright position and physical exercise are undoubtedly factors in certain cases Constriction of the renal vessels[18] through the injection of adrenalin and emotional excitement have been shown to produce albuminuria in experimental animals In humans similar factors may be operative our findings show that a

Certain writers suggest that this type of albuminuria is a stage in the recovery of an inflammatory process of the kidneys such as occurs in acute
tonsillitis but
related to a low
colds diseased

The determin
albuminuria will necessitate still further study but although this analysis shows that students with albuminuria are but little inferior physically to those whose urine contains no albumin it would seem as stated by Thorp and Wakefield[21] that the burden of proof rests with those who do not consider it due to renal injury

REFERENCES

1 ASHBURN P M 1928 An epidemic of albuminuria J Am Med Assn 90 535–539
2 BASHFORD, H H 1926 Adolescent albuminuria incidence s gmf
1905 307
1926 Albuminuria in
umin and album n with
millan Company
n experimental study of
Hopkins Hosp Rep 12
7 GOETZKY F 1910 *Zur Kenntnis der orthot schen Albuminurie* Jahrb f Kinderh 71 427–502
8 HESS H AND CALVIN J K Albuminuria in children, Med Clin North America 11 197 213
9 HILL, L C 1929 Febrile albuminuria with special reference to pneumonia Quart J Med 22 305–319

burg J, 173, 541-543
12 Moxon, W 1878 On chronic intermittent albuminuria, Guy s Hosp Rep, 23, 233-244
13 Palmer, R S 1931 Functional albuminuria, J Am Med Assn, 96, 1559-1562
14 Parmenter, W C 1920 Observations on the significance of functional albuminuria in young men at Harvard University, Boston Med and Surg J, 183, 677-681
15 Russell, J W 1925 The origin and significance of postural (ortho-

1157-1160
20 Teissier, J L 1899 Albuminurie de la station debout albuminurie orthostatique, Semaine méd, 19 425-427
21 Thorp, F G, and Wakefield, I G 1933 Orthostatic albuminuria, a comparison with other types of albuminuria Ann Int Med, 6 1565-1578

CHAPTER XXIX

ORTHOSTATIC PROTEINURIA *

By GRACE MEDES, Ph D and MARY NEEMES, B S

ETIOLOGY OF ORTHOSTATIC PROTEINURIA

SINCE 1870, when Ulzmann[25] reported 8 cases of proteinuria which could not be considered pathological, at least four general theories have been advanced to explain the predominant etiological factor in the so-called occasional or harmless proteinurias (1) Subnormal vascular development, (2) vasomotor instability, (3) general lowered condition, especially undernourishment and chronic infection, and (4) lumbar lordosis causing renal venous stasis That the kidney is not necessarily impaired is now generally accepted, nevertheless borderline cases are frequently reported and the question has remained unanswered as to whether or not there may be a gradation from harmless proteinuria to mild chronic nephritis The present study is an attempt to throw light on this point

No small part of the confusion in regard to the subject of harmless proteinuria seems to be due to the indiscriminate use of the large number of descriptive names applied to these proteinurias and the consequent assumption that they have a common etiology To recount a few such descriptive terms in general use, we have

(Dubreuilh[3]) and albuminuria of adolescents (Moxon[6]), although it was already known that protein might appear in the urine of healthy persons under certain special conditions, such as after cold baths and after violent exercise (Mahomed, quoted from Moxon)

Teissier[23] first used the term orthostatic albuminuria *for proteinuria* which appears when the subject is in the upright position, and Jehle,[11] in an exhaustive investigation demonstrated that in his cases these proteinurias were associated with chronic or assumed lordosis Nassau[17] recognized *two types the true lordotic* and a second which he called orthotic, following the terminology of

* Aided by grants from the Research fund of the Graduate Medical School of the University of Minnesota

Heubner,[8] wherein the proteinuria occurred in the upright position unassociated with lordosis Other investigators (i e, Post and Thomas[15]) have described a third type in which the proteinuria is

reappear He finds this type frequently following upon severe infections and it seems probable he is dealing with mild cases of nephritis in which the protein appears in the urine only when the subject is in the upright position A study of this group rightfully falls in the field of nephritis and possibly represents an extremely mild primary attack of nephritis in process of clearing up or of passing over to a latent period and characterized by an orthostatic proteinuria as the only sign

As early as 1878 Yeo[17] suggested vascular asthenia as the cause of occasional proteinuria, to explain its appearance in his patient after exercise and its disappearance after rest in bed or intake of food Following the frequent observation beginning with Clark[2] that alkalinization of the urine decreases the output of protein in

esses It is impossible even to cite all the attempts to explain the various orthostatic proteinurias on this basis Post and Thomas who first crystallized the idea believed failure to excrete protein upon alkalinization to be characteristic of all non nephritic cases and even suggested that the response to alkalinization might be made the criterion for differentiating them from the nephritic type By this test it may be possible to demonstrate a gradation from one to the other since Nassau[1] found in his studies that in the orthotic cases a much greater amount of alkali was required to decrease the output of protein than in the true lordotic type

Erlanger and Hooker[4] and Hooker Hegeman and Zartman[19] demonstrated that in their cases of orthostatic proteinuria the amount of protein excreted in the urine varied inversely with the pulse pressure Barach Bovee and Savage[6] found that the proteinuria exhibited by Marathon runners coincided in time with the post-exercise fall of pulse pressure and disappeared with the return of this factor to normal Hellebrandt Brogdon and Kelso[8] in a

authors found other instances of occasional proteinurias which followed violent and rapid muscular exercise but which were not related to variations of pulse pressure They explained these findings on the hypothesis that exercises of speed also bring about generalized systemic increase in acidity, altering the permeability of the renal cells to blood proteins in consequence of which albumin appears in the urine This explanation is essentially similar to that of Jervell[1] who explains the proteinuria following severe exercise by stasis and lactic acid accumulation He states that with a lactic acid content in the blood of more than 75 mg per 100 cc after physical exertion he always found albumin in the urine

Summary —Alteration in the alkalinity of the blood bathing the kidney cells probably is a factor in the production of many occasional proteinurias and has been used to explain orthostatic (including lordotic) proteinuria and the proteinurias following severe exercise and probably helps explain the decreased elimination following meals (alkaline tide) Blood flow (oxygen supply?) is probably also a factor *per se* the proteinuria decreasing during mild exercise and increasing when the blood flow is reduced as in marked stasis such as probably occurs in lordosis This factor of blood flow suggests a close relationship between these proteinurias and the proteinuria of nephritis in which decreased blood flow may play a predominant rôle It may also offer a partial explanation of the albuminurias in highly nervous young people where vascular instability may produce localized anoxemia The unsettled questions are how far are these changes in kidney permeability reversible, and is there a gradation from the reversible to the chronic stages?

Senator[21, 22] stood out among the early workers for the concept that all proteinurias have renal injury as a basis *More recently* point of view Thorp and proof rests with those who than renal injury and quote other investigators who tend to this point of view They divide their cases into (1) Orthostatic albuminuria, (2) albuminuria with orthostatic response, (3) latent and (4) chronic glomerulonephritis Seventeen out of 143 cases in (1) and (2) probably dated from acute nephritis Four cases out of 100 in the first group showed definite signs of nephritis or progressed to it They suggest the following explanation In accordance with previous findings (*i e* White Rosen Fischer and Wood[5]) water and such substances as urea are excreted more easily in the recumbent position In mild renal injury albumin may not be excreted in this position whereas as soon as the upright *position is* assumed the kidney is not able to adjust itself and loss of albumin results In *support of this view* they show that in chronic glomerulonephritis the element of orthostatic response disappears as the disease pro-

gresses Therefore, they conclude that orthostatic albuminuria is probably in the range of mild pathological physiology

In accordance with this point of view, lordotic proteinuria (proteinuria which appears when the subject is in the lordotic position and disappears when he resumes any other posture) might be looked upon as an even milder injury since the kidney is able to adjust itself to the upright position and requires an additional strain to induce the proteinuria Very little work has been done with rigidly selected cases of the purely lordotic type upon which a conclusion on this point may be reached The authors have, therefore undertaken the following study

STATISTICAL STUDIES OF LORDOTIC PROTEINURIA

For comparison there are included studies of two other groups, normal individuals and individuals with constant proteinuria, classed as follows (1) Normal individuals (2) individuals with mild lordotic proteinuria (3) individuals with severe lordotic proteinuria (4) individuals with constant proteinuria The dividing line between Groups 2 and 3 was often decided upon with some difficulty but all cases in which urinary protein was present in sufficient amounts to be estimated quantitatively were placed in Group 3 although some slight discrepancies may have occurred on account of differences in the degrees of diuresis Thirteen to 21 individuals were included in each group All were between eighteen and twenty-four years of age The control subjects in

through the courtesy of Drs Diehl and Radl Only a few were underweight or of the so-called lordotic build No attempt was made to correlate these two factors with the phenomenon being investigated since previous studies of this relationship seemed adequate (See Chapter XXVIII by Diehl and McKinlay) The control subjects in Group 4 comprised a miscellaneous group of ambulatory patients in the University of Minnesota Hospital and University Health Service all of whom had been diagnosed as having chronic nephritis Most of them were in an early stage of nephritis Two were in advanced stages

Rehberg's creatinine-clearance test of glomerular filtration[19] was employed in the functional studies and was conducted as follows The subject was given 3 gm of creatinine by mouth and was kept in a recumbent position for one hour Following this the test was carried out with the individual in the four following positions (a) Recumbent kyphotic (thirty minutes) (b) standing kyphotic (twenty minutes) (c) standing lordotic (twenty minutes) (d)

standing kyphotic (twenty minutes) For statistical comparison with (*c*) the values of (*b*) and (*d*) were averaged (*e*)

Blood samples were taken at the beginning of Period 1 and at the close of each subsequent period Urine was collected quantitatively at the end of each From the concentrations of creatinine in these samples and the urinary volumes the minute glomerular filtrations (creatinine clearances) were figured by Rehberg s method Protein when present in sufficient amounts was estimated by precipitating with trichloracetic acid and subsequent ashing by Folin s micro-Kjeldahl method

TABLE 61 RESULTS OF REHBERG S TEST OF GLOMERULAR FILTRATION ON 7 INDIVIDUALS INCLUDING NORMAL SUBJECTS (1) SUBJECTS WITH MILD AND HEAVY LORDOTIC PROTEINURIA (2 AND 3) AND SUBJECTS WITH CONSTANT PROTEINURIA (4) THE VALUES FOR THE MEANS AND THE STANDARD DEVIATIONS TOGETHER WITH THEIR RESPECTIVE PROBABLE ERRORS ARE GIVEN FOR TESTS IN RECUMBENT (*a*) KYPHOTIC (*b* AND *d*) AND LORDOTIC POSITIONS (*c*) IN COLUMN *e* ARE GIVEN THE SIMILAR STATISTICAL COMPUTATIONS FROM THE AVERAGES OF THE TWO FILTRATION VALUES OBTAINED IN THE STANDING KYPHOTIC POSITION

Group	No of subjects	Glomerular filtration cc per minute				
		a Recumbent 30 minutes	*b* Standing kyphosis 20 minutes	*c* Standing lordosis 20 minutes	*d* Standing kyphosis 20 minutes	*e* Standing kyphosis average
		Mean ± P E$_M$				
1	20	170 8 ± 4 3	171 4 ± 4 2	166 8 ± 4 7	168 5 ± 3 8	169 8 ± 5 0
2	21	158 5 ± 4 8	159 1 ± 5 9	152 8 ± 6 9	154 7 ± 8 7	153 9 ± 5 4
3	18	155 5 ± 7 0	159 0 ± 7 2	101 9 ± 8 7	148 5 ± 8 3	157 4 ± 6 6
4	13	137 5 ± 11 6	131 0 ± 9 6	98 5 ± 10 2	115 2 ± 11 1	120 5 ± 8 6
		Standard Deviation ± P E$_{SD}$				
1	0	27 6 ± 2 9	26 7 ± 2 9	30 3 ± 3 3	24 7 ± 2 7	21 7 ± 2 4
2	21	31 9 ± 3 5	37 8 ± 4 1	46 0 ± 5 9	36 0 ± 6 1	35 6 ± 3 8
3	18	41 7 ± 5 0	42 7 ± 5 1	51 4 ± 6 1	45 7 ± 5 6	39 3 ± 4 7
4	13	59 4 ± 8 2	47 1 ± 6 8	5 1 ± 7 2	44 2 ± 7 8	44 5 ± 6 1

Glomerular Filtration —Results of the functional studies are embodied in Table 61 The mean creatinine clearance in the group of individuals without proteinuria was 170 8 ± 4 3 cc per minute with a range of 121 to 208 cc per minute Between the mean filtrations of this group and of that with mild lordotic proteinuria there was a difference of 12 3 cc per minute This difference is not of statistical significance the ratio of the difference between the two means to its probable error being 1 9 The same general statement may be applied to a comparison of the filtrations of Groups 1 and 3 in which the lordotic proteinuria was quantitatively

greater The corresponding ratio is also 1 9 The mean glomerular filtration of Group 4 was 137 5 cc per minute Here, because of the high probable error consequent upon the heterogeneous grouping, the ratio of the difference between the means of Groups 1 and 3 to its probable error is scarcely of statistical significance being 2 7

In no case is there a significant difference between the creatinine clearances in the recumbent and in the standing kyphotic positions In all groups except Group 4 the value was almost the same during the two periods in this latter posture This finding is in apparent contradiction to that of Rehberg[20] that glomerular filtration is lower in the upright position It may be noted however, that his experiments were made following periods of activity whereas these tests had been preceded by ninety-minute periods of rest in bed

The average values of *b* and *d* are given in column *e* (Table 61) Between the means of the filtrations in the kyphotic and in the lordotic positions (columns *e* and *c*) there is no statistically significant difference in Groups 1 2 and 4 In Group 3 the ratio of the difference between the means to its probable error rises to 4 7 and therefore indicates that a fall in clearance in individuals with heavy lordotic proteinuria is a fundamental characteristic of the phenomenon In 3 individuals of the group however the decrease was negligible whereas in 1 case the clearance fell from 256 cc to 44 cc per minute There was no such extreme fall among the normal individuals here the greatest drop was from 238 cc to 134 cc per minute In Group 4 the largest drop was from 64 to 9 Among the normal subjects the lowest rate of filtration during lordosis was 111 a value at approximately the low limit of normal Among the individuals of Group 3 the range was from 36 to 208 demonstrating that while some of these individuals have normal filtration rates even during lordosis others while in this attitude are characterized by rates comparable to subjects with advanced nephritis

The majority of other workers have not reported any marked differences in functional tests between individuals with and those without lordotic proteinuria An exception may be made in the case of Hempelmann[7] who reports a decrease in the phthalein output in orthostatic albuminuria He used children of a marked lordotic build all having heavy proteinuria and compared them with 2 normal children In all his observed cases there was a decreased output of phthalein in the lordotic position as contrasted with an unchanged output in normal children The smaller number of his normal subjects together with the extreme lordotic type of his experimental cases does not allow any conclusions to be drawn as to gradations from normal to postural proteinuria and from postural to the mild constant type

That individuals who have proteinuria in the lordotic position

give a more varied test than the control (Group 1) is shown by the relatively higher standard deviations as indicated in Table 61 This applied to all postures which the subjects assumed The variability of the control individuals is not significantly increased by change of posture nor is that of those with constant proteinuria whereas in both experimental Groups 2 and 3 the standard deviations increase in the lordotic positions though not sufficiently to attain statistical significance

Protein Output —*Posture* —*Attempts to correlate fall in creatinine clearance upon assumption of the lordotic position with quantity of protein excreted by the individuals in Group 3 demonstrated that there* is no positive correlation between the two phenomena The fall in clearance varied from 9 to 180 cc per minute or from 7 to 83 per cent The excretion of protein varied from 6 to 231 mg during the twenty minutes of lordosis The coefficient of correlation between these two sets of data is +0 3 which is without sig*nificance in a group of 18 No correlation could be demonstrated* between the amount of protein excreted and volume of glomerular filtrate either in the resting or in the lordotic position A possible explanation for this lack of correlation is discussed later

In Group 4 the output of protein was for the most part constant regardless of posture In 2 individual cases however a marked *increase occurred In 1 subject the protein output rose from* 30

per minute) in the second it decreased from 133 to 71 cc per minute In general then in true nephritis the output of protein *is* constant regardless of posture in an occasional case lordotic proteinuria may be superimposed and may or may not be accompanied by fall of filtration through the kidney

Medes a[illegible] t in individuals [illegible] 47 cc per minu[illegible] ute The range was from 29 4 to 100 3 cc per minute These values are in approximate agreement with those of the subjects of this study having mild lordotic proteinuria (see Table 61 Group 2) and differ from those with heavy proteinuria principally in their smaller *probable error of the mean and standard deviation* Medes and Berglund found a statistically significant difference between the means of this group of mild proteinurias and their normal subjects *whose filtrations averaged* 172 9 ± 2 9 cc per minute The lower probable error in their control group was due to the larger number comprising it and indicates that with sufficiently large groups the differences between *the filtration* of the control subjects of this

study and of those with lordotic proteinuria might have been of statistical significance

Alkalinization and Acidification of the Urine — Attempts were made to find other factors that might influence the amount of protein excreted while the subject stood in the lordotic position Exercise and protein intake produced no effect The effect of alkalinization of the urine noted by Post and Thomas[13] was confirmed These authors found in a series of subjects with orthostatic albuminuria that protein failed to appear when the urine was alkalinized whereas proteinuria could not be inhibited by this [illegible]

former instance the output of protein was increased a much greater extent upon acidification and reduced to zero upon alkalinization In the latter case the output could not be reduced below 3 1 mg per ten minute period

TABLE 62 — EFFECT OF ALKALINITY AND ACIDITY OF THE URINE ON PROTEIN OUTPUT DURING LORDOSIS IN (A) LORDOTIC PROTEINURIA AND (B) CHRONIC NEPHRITIS THE PROTEIN OUTPUT WAS ESTIMATED PER TEN MINUTE PERIOD

A Lordotic proteinuria				B Chronic nephritis			
Day of exper	Feeding	pH of urine	Protein mg	Day of exper	Feeding	pH of urine	Protein mg
1		6 7		1		6 7	15 0
2		6 5			1 5 gm $NaHCO_3$	6 0	13 7
3	3 gm KH_2PO_4	5 2	1 [illegible]		1 5 gm $NaHCO_3$	5 7	3 1
4	3 gm $NaHCO_3$	5 8	9 4		3 0 gm $NaHCO_3$	5 8	5 1
	3 gm $NaHCO_3$	7 6	3 6		3 0 gm KH_2PO_4	5 4	27 8
5	3 gm $NaHCO_3$	7 6	2 6	3	1 5 gm $NaHCO_3$	6 6	12 0
7	3 gm $NaHCO_3$	7 7			3 0 gm $NaHCO_3$	7 0	3 8
	3 gm KH_2PO_4	7 0	3 3		3 0 gm $NaHCO_3$	7 [illegible]	3 2
8	3 gm KH_2PO_4	5 2	18 8		3 0 gm $NaHCO_3$	7 [illegible]	3 5
9	3 gm $NaHCO_3$	5 0	47 0		3 0 gm KH_2PO_4	5 8	15 0
10	3 gm $NaHCO_3$	6 3	17 4				
11	3 gm $NaHCO_3$	6 8	8 4				
12	3 gm $NaHCO_3$	6 8					

Change of reaction of the urine with consequent alteration in the amount of protein excreted did not affect the value of the minute filtration in any one individual In one subject for instance, when the urine was alkalinized the glomerular filtration while he was [illegible]

tions in protein output probably explains the low correlation between filtration and loss of protein in Group 3 It also opens the question of the validity of any classification of these individuals on the basis

of amount of protein excreted during lordosis But in view of the fact that we found at least *one fundamental difference* between Groups 2 and 3 namely that in Group 3 rate of filtration was markedly affected by change of posture whereas in the group of mild proteinurias (Group 2) no such relationship could be demonstrated we must conclude that even though individuals vary widely on the average a marked fall in glomerular filtration may be expected to be associated with a high protein output during lordosis

Summary and Conclusions The rates of glomerular filtration of 78 individuals between the ages of eighteen and twenty four years were determined by Rehberg s method

The first group consisting of 20 normal individuals was found to have a mean rate of filtration of 170 8 ± 4 3 cc per minute while in the recumbent position The rate was not significantly changed upon their standing either in a kyphotic or in a lordotic position

The second group consisted of 21 individuals whose urines were free of protein except for traces when they assumed a position of extreme lordosis Their mean rate of filtration (recumbent position) was 158 5 ± 4 8 cc per minute Statistically considered the difference between the rat [illegible]
significant but wou [illegible]
group been tested [illegible]
change of posture

The third group consisted of 18 subjects who differed from those of Group 2 only in their heavier proteinuria when in the lordotic position Their mean rate of glomerular filtration was approximately the same as that of the previous group 155 5 ± 7 0 cc per minute *In contrast to the previous cases their mean rate of filtration was affected by posture* falling to 101 9 ± 8 7 cc per minute when they stood in a lordotic position

The fourth group consisted of ambulatory patients in various stages of chronic glomerulonephritis Their mean rate of glomerular filtration was 137 5 ± 11 6 per minute It fell to 98 5 ± 10 2 cc per minute upon their assuming a lordotic posture but the high probable error due to the small number of subjects and the wide variations in their individual filtration rates made this difference of low statistical significance

The amount of protein excreted by subjects in Group 3 showed only a slight positive correlation with decrease in rate of glomerular filtration when these individuals assumed a lordotic posture This low correlation might possibly be explained by the fact that the amount of protein excreted varied with the reaction of the urine the proteinuria disappearing upon extreme alkalinization and reappearing upon acidification

These quantitative changes were not characteristic of individuals

with chronic nephritis In this group the amount of protein excreted varied somewhat with reaction but to a less extent In individuals with mild chronic nephritis the variability was greater than in those in advanced stages

In general individuals with lordotic proteinuria show some transitional characteristics between normal subjects and those with chronic nephritis in the following respects

(*a*) Their mean rate of glomerular filtration is somewhat lower than that of normal individuals

(*b*) Their filtration rates when they stand in the lordotic position vary from well within the normal range (over 100 cc per minute) to a rate characteristic of severe nephritis

(*c*) Their variability as shown by the standard deviations of their filtration rates increases from normal subjects through individuals subject to lordotic proteinuria to patients with chronic nephritis In normal individuals this variability was not increased by change of posture In the group with mild lordotic proteinuria the variability approached and in the group with severe lordotic proteinuria it equaled that of the patients with severe nephritis

References

1 Barach Boyce and Savage, quoted from Hooker D R 1910 Arch Int Med 5 508

2 Clark Sir Andrew 1884 On albuminuria Brit Med J 11 312

3 Dubreuilh, W 1857 Revue critique de l albuminurie intermittente périodique Rev de méd 7 678–691

7 Hempelmann T C 1915 The phthalein test in orthostatic albuminuria Am J Dis Child 10 418–421

8 Heubner, O 190 Zur Kenntnis der orthotischen Albuminurie Berl klin Wchnschr 44, 1–4

9 Hooker D R 1910 Postural or orthostatic albuminuria A critical summary of the literature Arch Int Med 5 491–509

10 Hooker D R Hegeman R F Zartman L V 1908 1909 The relation of pulse pressure to the appearance of albumin in a case of orthostatic albuminuria Am J Physiol 23, xi

11 Jehle, L 1932 Lordotische Albuminurie Wien med Wchnschr 82 1215 1216

k Mag f Lægevi
1929

weiss im Harn des
157

ehberg s creatinine

Med Sci n s 128

16 Moxon W 1878 On chronic intermittent albuminuria, Guy s Hospital Rep 23 233 244

of amount of protein excreted during lordosis But in view of the fact that we found at least one fundamental difference between Groups 2 and 3 namely that in Group 3 rate of filtration was markedly affected by change of posture whereas in the group of mild proteinurias (Group 2) no such relationship could be demonstrated we must conclude that even though individuals vary

78 individuals between the ages of eighteen and twenty four years

was found

per minute

while in the recumbent position The rate was not significantly *changed upon their standing either in a kyphotic or in a lordotic* position

The second group consisted of 21 individuals whose urines were free of protein except for traces when they assumed a position of extreme lordosis Their mean rate of filtration (recumbent position) was 158 5 ± 4 8 cc per minute Statistically considered the differ

change of posture

The third group consisted of 18 subjects who differed from those of Group 2 only in their heavier proteinuria when in the lordotic position Their mean rate of glomerular filtration was approximately the same as that of the previous group 155 5 ± 7 0 *cc per* minute In contrast to the previous cases their mean rate of filtration was affected by posture falling to 101 9 ± 8 7 cc per minute when they stood in a lordotic position

The fourth group consisted of ambulatory patients in various stages of chronic glomerulonephritis Their mean rate of glomerular filtration was 137 5 ± 11 6 per minute *It fell to* 98 5 ± 10 2 *cc* per minute upon their assuming a lordotic posture but the high probable error due to the small number of subjects and the wide variations in their individual filtration rates made *this difference of low statistical significance*

The amount of protein excreted by subjects in Group 3 showed only a slight positive correlation with *decrease in rate of glomerular* filtration when these individuals assumed a lordotic posture This low correlation might possibly be explained by the fact that the amount of protein excreted varied with the *reaction of the* urine the proteinuria disappearing upon extreme alkalinization and reappearing upon acidification

The e q antitative changes were not characteristic of individuals

with chronic nephritis In this group the amount of protein excreted varied somewhat with reaction but to a less extent In individuals with mild chronic nephritis the variability was greater than in those in advanced stages

In general individuals with lordotic proteinuria show some transitional characteristics between normal subjects and those with chronic nephritis in the following respects

(*a*) Their mean rate of glomerular filtration is somewhat lower than that of normal individuals

(*b*) Their filtration rates when they stand in the lordotic position vary from well within the normal range (over 100 cc per minute) to a rate characteristic of severe nephritis

(*c*) Their variability as shown by the standard deviations of their filtration rates increases from normal subjects through individuals subject to lordotic proteinuria to patients with chronic nephritis In normal individuals this variability was not increased by change

REFERENCES

1 BARACH BOYCE AND SAVAGE quoted from HOOKER D R 1910 Arch Int Med 5 508

7 HEMPELMANN T C 1915 The phthalein test in orthostatic albuminuria Am J Dis Child 10 418–424

8 HEUBNER O 1907 Zur Kenntnis der orthotische Albuminurie Berl klin Wchnschr 44 1–4

9 HOOKER D R 1910 Postural or orthostatic albuminuria A critical summary of the literature Arch Int Med 5 491–509

10 HOOKER D R HEGEMAN R I ZARTMAN L V 1908 1909 The relation of pulse pressure to the appearance of albumin in a case of orthostatic albuminuria Am J Physiol 23 xi

11 JEHLE L 1932 Lordotische Albuminurie Wien med Wchnschr 82 1245–1246

Norsk Mag f Lægevi n 92 69? 1929
von Eiweiss im Harn des 2, 145–157
s in Rehberg s creatinine

m J Med Sci n s 128

16 MOXON W 1878 On chronic intermittent albuminuria Guy s Hospital Rep 23 233 244

of amount of protein excreted during lordosis But in view of the fact that we found at least one fundamental difference between Groups 2 and 3 namely that in Group 3 rate of filtration was markedly affected by change of posture whereas in the group of mild proteinurias (Group 2) no such relationship could be demonstrated we must conclude that even though individuals vary

78 individuals between the ages of eighteen and twenty four years were determined by Rehberg s method

The first group consisting of 20 normal individuals was found to have a mean rate of filtration of 170 8 ± 4 3 cc per minute while in the recumbent position The rate was not significantly changed upon their standing either in a kyphotic or in a lordotic position

The second group consisted of 21 individuals whose urines were free of protein except for traces when they assumed a position of extreme lordosis Their mean rate of filtration (recumbent position) was 158 5 ± 4 8 cc per minute Statistically considered the difference between the rates of these two groups was found to be scarcely significant but would probably have been significant had a larger group been tested Their mean rate of filtration was unaffected by change of posture

The third group consisted of 18 subjects who differed from those of Group 2 only in their heavier proteinuria when in the lordotic position Their mean rate of glomerular filtration was approximately the same as that of the previous group 155 5 ± 7 0 cc per minute In contrast to the previous cases their mean rate of filtration was affected by posture falling to 101 9 ± 8 7 cc per minute *when they stood in a lordotic position*

The fourth group consisted of ambulatory patients in various stages of chronic glomerulonephritis Their mean rate of glomerular filtration was 137 5 ± 11 6 per minute It fell to 98 5 ± 10 2 cc per minute upon their assuming a lordotic posture but the high probable error due to the small number of subjects and the wide variations in their individual filtration rates made this difference of low statistical significance

The amount of protein excreted by subjects in Group 3 showed *only a slight positive correlation* with decrease in rate of glomerular filtration when these individuals assumed a lordotic posture This low correlation might possibly be explained by the fact that the amount of protein excreted varied with the reaction of the urine

CHAPTER XXX.

PROTEINURIA AND PLASMA PROTEINS *

By HILDING BERGLUND, M D , WALTER DE M SCRIVER, M D ,

AND

GRACE MEDES, PH D

lated
with
fact

was well known[16] that certain urines contained a substance which coagulated "like diluted serum of the blood" when a tablespoonful *of urine was heated over the candle flame Blackall [8] in 1813*, brought out the fact that this was particularly the case in dropsies which occurred after scarlatina and likewise after treatment of lues venerea with mercury That hematuria occurs in some patients, "when the body swells after scarlatina," had been observed still earlier by von Rosenstein,[65] a Swedish pediatrician The signifi-

kidneys" and about Blackall s conclusion on heat-coagulable urine "Whether the blood is presented for secretion in a vitiated state or the urinary organs themselves perform their office imperfectly is at present not well ascertained Through the work of Bright

bring the question no further than to point out the presence of a marked dilution of the blood serum in some of his patients

The development of protein chemistry was the condition for further progress Though the separation of the chief blood proteins by precipitation with different salts was accomplished about

* From the Biochemical Laboratory of Harvard Medical School the Medical Service of the Peter Bent Brigham Hospital Boston and the Department of Medicine and the Medical Service of the University Hospital University of Minnesota Minneapolis Minn Partially aided by a grant from the Medical Research Fund of the University of Minnesota. Dr Scriver as a National Research Council fellow was a collaborator in the work during the Boston period Dr Medes during the Minnesota period

17 NASSAU, E 1922 Ueber die Bedeutung der Reaktion des Harns fur das Auftreten der statischen Albuminurien im Kindesalter, Ztschr f Kinderh, **33**, 158–168

18 POST, W E, AND THOMAS, W A 1923 Orthostatic Albuminuria, J Am Med Assn, **80**, 293 299

19 REHBERG, P B 1929 Ueber die Bestimmung der Menge des Glomerulusfiltrats mittels Kreatinin als Nierenfunktionsprufung, nebst einigen Bemerkungen uber die Theorien der Harnbereitung, Zentralbl f inn Med, No 15, pp 1–11

20 ———— 1929 The influence of posture on kidney function, Abs XIIIth Int Physiol Congress, Am J Physiol, 90, 491

CHAPTER XXX.

PROTEINURIA AND PLASMA PROTEINS *

By HILDING BERGLUND, M D WALTER DE M SCRIVER, M D,

AND

GRACE MEDES PH D

lated
with
fact
was well known[16] that certain urines contained a substance which coagulated like diluted serum of the blood when a tablespoonful of urine was heated over the candle flame Blackall,[8] in 1813, brought out the fact that this was particularly the case in dropsies which occurred after scarlatina and likewise after treatment of lues venerea with mercury That hematuria occurs in some patients, "when the body swells after scarlatina,' had been observed still earlier by von Rosenstein[65] a Swedish pediatrician The signifi-

or the urinary organs themselves perform their office imperfectly is at present not well ascertained Through the work of Bright the theory was abandoned which attributed the cause of albuminuria to the condition of the blood (hematogenous albuminuria), and the theory was introduced according to which the kidney constitutes the determining factor (nephrogenous albuminuria) Bright did not loose sight of the problem of the blood in nephritis but could bring the question no further than to point out the presence of a marked dilution of the blood serum in some of his patients

The development of protein chemistry was the condition for further progress Though the separation of the chief blood proteins by precipitation with different salts was accomplished about

* ... the Minnesota period

the middle of the last century, it was the "salting-out' methods of Hammarsten[35] and Hofmeister[41] that led to a systematic attack upon the urinary proteins Hofmeister studied the occurrence of lower proteins, albumoses and peptones in human urine Earlier, in 1866, Lehmann [66] of Copenhagen, had tried by dilution and saturation with carbon dioxide to demonstrate the presence of small amounts of globulin in every albuminous urine Senator,[69] in somewhat voluminous writings, inquired into the relationship between serum albumin and globulin in urines, expecting to find cases where globulin alone was excreted—the globulin according to Kuhne being more diffusible than the albumin Through the work of Hoffmann[19] it seemed established that the ratio between serum albumin and globulin in the urine from nephritic patients is rather variable that the albumin prevails sometimes to the extent of giving ratios as high as 10 to 1 Hoffmann pointed out the difference between this distribution and the distribution in normal blood serum and in transudates like ascites fluid [40] In so doing, Hoffmann was unaware of the abnormal ratios in opposite direction which commonly exist in the blood of these patients making the contrast more marked From 22 nephritic cases Hoffmann concluded that the albumin to globulin quotient was independent of [illegible] *but believed himself*
of the
turb
cord
and

determining by weighing the globulin precipitate

Among later contributions the careful work of Csatáry[17] [18] shall be mentioned carried out with Hofmeister s[41] method The albumin to globulin quotients found by Csatary correspond well with the ones reported by Hoffm [illegible]
taining only globulin
any globulin was found
globulin content with a quotient sometimes *lower than unity* Other types of nephritis gave quotients varying between a little more than unity and as much as 8 Intercurrent fevers increased the relative amount of globulin excreted *Csatáry, like Hoffmann,* considered a diminution of the globulin a favorable sign

There exists a fair amount of work from the eighties and nineties [illegible] are confusing *The original methods of*
edious Thus simplifi
educed or lost Great

errors may have entered through *inaccurate adjustment* of the reaction of the system in the salting out process The importance of a neutral or amphoteric reaction had been found and emphasized by Hammarsten and by Hofmeister There *is reason to suspect*

that in the hands of some workers overneutralizations occurred and made the "globulin" disappear and there is no doubt that the large amounts of "globulin" reported by Boyd [10] for instance were due to acidification with acetic acid during the fractionation A similar error entered into the work of Estelle [28]

The question as to the occurrence of fibrinogen or fibrin in albuminous urine now presents itself Limiting our inquiry to nephritic conditions we know spontaneous coagulation of urine to be a rare finding in nephritis caused by the use of cantharidin plaster [69] According to Senator who seems first to have observed this condition serum albumin and globulin are present besides fibrin

The question as to the amount of protein lost with the urine in acute and chronic kidney diseases and particularly the factors influencing the loss seems a simpler problem than the albumin globulin question The problem has hardly been tackled in a quantitative way There are clinical studies as to the merits of white or red meat and the effect of a straight milk diet But whether 1 liter of milk gives less albuminuria than 3 liters the literature does not reveal *

So far we have dealt with protein in urines secreted by diseased kidneys As a transition to instances where protein passes through normal kidneys we meet with paroxysmal hemoglobinuria described by Dressler [21] about the middle of the last century The speed of elimination and the degree of concentration of hemoglobin by the kidney [66] are great Clinical and experimental observations show that albuminuria always accompanies and outlasts a hemoglobinuria Permanent kidney injury does not seem to develop even after years of repeated attacks [67] Interest has long been given to the excretion of the protein which was described by Bence-Jones [4] in 1847 and which carries his name This is discussed by one of us in Chapter XXI Spontaneous crystallization of protein in urine is a rare phenomenon and does not always signify Bence-Jones proteinuria This is exemplified by a unique condition extensively and convincingly studied by Paton In this case with histologically normal kidneys and with no clinical symptoms of nephritis over a period of years enormous quantities were excreted of a protein which crystallized spontaneously from the urine in crystals like egg albumen Paton determined the protein as a globulin No signs of malignancy were found at the autopsy Another interesting but obscure instance of globinuria has been described by Batty [5] and Wallis [75b]

The types of proteinuria just referred to the hemoglobinuria and the Bence-Jones proteinuria might well be labeled hematogenous Their discovery in the middle of the nineteenth century

* Csatáry to be sure observed an unmistakable increase in proteinuria after feeding a nephritic large amounts of soft boiled eggs for two days

aroused interest in the experimental production of similar conditions Hence much work was reported on the occurrence of egg albumen in the urine after the taking of raw egg white by mouth and after parenteral administration The general criticism of the work with foreign proteins should be directed toward the methods used in ascertaining what kind of protein appeared in the urine Efforts to correlate the experimental facts under a general viewpoint have not been wanting The biological view held by Abderhalden accrediting the kidney with distinguishing and eliminating *blut fremde* proteins retained its popularity until the present dominance of the physical-chemical aspects of the blood colloids

RELATIONSHIP BETWEEN PROTEIN METABOLISM AND PROTEINURIA

The authors work was begun under the impression that no conclusions could be drawn from the older literature concerning the relationship between albumin and globulin in nephritic urines Not that the older results necessarily were incorrect but without new work taking recent development of protein chemistry into consideration an evaluation of the early results did not seem possible Ahead of the problem of the nature of the urinary proteins an inquiry into the factors which influence or determine their elimination seemed wanted

A suitable method for the fractionation and determination of urinary proteins had to be worked out The method finally arrived at[5] for fractionation uses Na_2SO_4 essentially in the concentrations used by Howe and applies the same principle for the fractionation and determination to both blood and urine This we consider not only a convenience but a theoretical advantage

In choosing the material for the study animal experimentation at least under the authors hands yielded relatively little After feeling around in different directions patients with practically unimpaired nitrogen elimination and with large amounts of urinary proteins became the first subjects for investigation Thus most of the patients used for metabolic experiments were instances of nephrosis The material on hand is presented independently of the chronological order in which it might have been worked up First is presented detailed experiments on a few individuals partly the experiments may be termed metabolic Then a description of ... pathologi... ...tion of ... ate the ... ntration

de[illegible]

in [illegible]

amount of protein in the urine

Reverting to the early concepts briefly sketched above, there are presented some experiments exemplifying the *hematogenous* factor in albuminuria, followed by others where the *nephrogenous* factor might be the determining one or where it is impossible at present to decide between the two

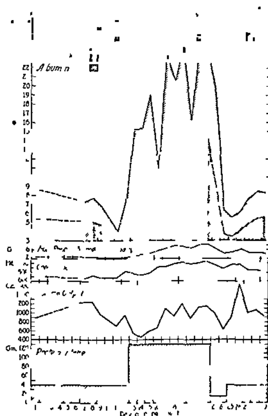


FIG 99 —Relation between level of protein intake and elimination of urinary protein Mr Bsi Nephrosis

The Relation Between the Level of Protein Metabolism and Proteinuria *—1 The results of the first experiment to elucidate this relationship are strikingly shown in Fig 99 The subject, Mr Bsi, had been sick with heavy albuminuria and edema of

* The authors use this opportunity gratefully to acknowledge the painstaking cooperation of the dietetic services of the Peter Bent Brigham Hospital Boston Mass and the University Hospital Minneapolis Minn

varying intensity for more than a year Most of this time his *protein intake had been restricted* During the first period of the experiment, when the protein intake was calculated as 40 gm daily and the total calories as 2500, the plasma proteins were determined as 4 83 and 4 47 per cent, the albumin in the latter sample amounting to 0 95 per cent only During this period the urinary (non-protein) nitrogen varied between 2 2 and 2 8 *gm daily and the*
proteinur four
hours was
no nitrog tein
diet calc otal
calories was followed by the large increase in urinary proteins, which constitutes the chief feature of this and following experiments The increase was prompt, the proteinuria rising from 7 55 gm pro*tein on the last day of the low diet to 15 3 gm during the first*
t
t

in the curve During the high diet daily observations of the urinary sediment failed to reveal any signs of acute renal irritation On the ninth day of the high diet diarrhea developed on the eleventh day the diet was changed to rice water, tea, toast and sugar, representing about 15 gm protein and 500 Calories, *which after another* day was followed by the 40-gm protein diet from the foreperiod The institution of two days of low diet was accompanied by an abrupt fall in urinary
6 39 gm only On
urinary proteins ret
behavior of the urinary (non-protein) nitrogen during the high protein diet, rising slowly to a maximum of 8 3 gm only, clearly indicated a positive balance *Compared with the magnitude of* this balance the rise of the non-protein nitrogen level of the blood was insignificant it rose from 25 2 to 54 5 mg per 100 cc plasma The gain from the positive nitrogen balance is reflected in the increase of plasma proteins the total proteins rose from 4 47 to 5 75 per cent in ten days and the albumin from 0 95 to 1 7 per cent in sixteen days The body weight first increased from 63 8 kg on the first day of the experiment to 66 kg on the nineteenth day, whereupon it fell to 60 6 kg *on the last day*, the twenty ninth The patient was confined to bed during the whole experiment The same holds for all subsequent experiments unless otherwise stated

2 It was thought worth while to repeat the experiment on the same patient at a later occasion Thus, after the summer vacation in 1925 the observations presented in Fig 100 were made At present we wish to consider only the first thirty days of the experi-

ment. The plan for this period was the same as in Fig. 99, with the modification that the high protein diet was continued for twenty-two days The results confirmed the first experiment in every way. The increase in urinary proteins during the high diet took place more gradually, but *the peak reached before the diet*

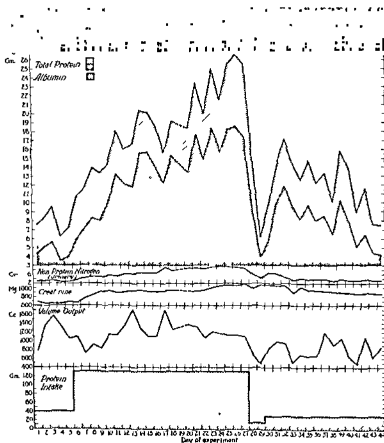


Fig. 100 —Elimination of urinary protein as influenced by (*a*) level of protein intake (*b*) fever and (*c*) blood transfusion Discussion on pages 478 and 479 Mr Ba Nephrosis

was altered was higher the maximum twenty-four-hour output being 26.6 gm *versus* an average of 7.8 gm during the foreperiod The decline in protein output following the change in diet was as abrupt and far-going as in Fig 99, the protein elimination during the twenty-eighth and twenty-ninth day (Fig 100) being 15.22 and

6 15 gm , respectively As in the preceding experiment a positive nitrogen balance existed the [illegible]

Table 63 — Albumin in Per Cent of Total Urinary Protein During Different Levels of Protein Intake Mr Bst Nephrosis

Dietary condition	Albumin content of urinary protein		
	Mean ± P E	σ	
I Five days foreperiod on 40 gm protein daily	58 0 ± 0 73	2 15	
II First five days on 130 gm protein daily	61 3		
III Subsequent twelve days on same diet	75 4 ± 0 50	[illegible] 48	I Difference between mean III and mean I of high significance ratio between difference and probable error of difference = 19 7
IV Last five days on high diet	71 0		
I IV Whole period of high diet	71 2 ± 0 97	6 58	II IV Difference between mean II IV and mean I significant ratio between difference and probable error of difference — 11 3
V First three days on subsequent low diet 15 to 30 gm protein daily	62 8 ± 1 40	2 94	V Difference between mean II–IV and mean V significant ratio between difference and probable error of difference = 4 93

The experiment further provides a continuous record of the relation of albumin to globulin in the urine (Table 63) During the foreperiod the albumin constituted an average of 58 per cent of the urinary protein during the high diet this ratio gradually changed, so that during the eleventh to the twenty second day of [illegible]

tinuation of the high diet the albumin was reduced more than the globulin the albumin falling to 62 8 per cent of the total protein

In number of grams of protein excreted this patient among all studied showed the greatest response to the experimental condition

The positive nitrogen balance likewise was more marked than in any other patient The experiments so far reported clearly bring out the independence of the proteinuria of the level of the protein metabolism if measured by the urinary (non protein) nitrogen, but its dependence on the level of the protein intake

3 The following 5 experiments were carried out in order fully to establish the relationship between protein intake and proteinuria The experiment presented in Fig 101 pertains to a young girl, Miss

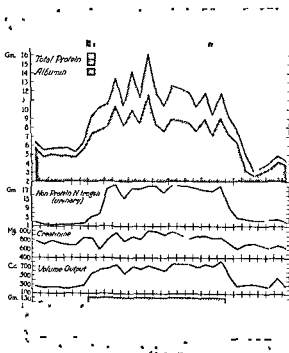


Fig 101 Relation between protein metabolism and protein elimination Miss Kx Nephrosis

Kx aged sixteen years, with a typical nephrosis The circumstances in this experiment in one respect differ from the previous

nitrogen of the plasma from 23 to 56 mg during the high diet must

not be
caloric
and 20
daily The weight at the beginning of the experiment was 54 5 kg at its end 50 kg the drop was gradual

The urinary protein response to the changed protein intake was

of the high diet The decline of the proteinuria at the end of the high diet was prompt The total increase in proteinuria was smaller than in the first patient in spite of essentially identical conditions in diet and protein output during the foreperiod

The ratio between albumin and globulin differs from the ratio in the first patient During the foreperiod the albumin constituted 87 1 ± 0 52 per cent of the urinary protein during the high diet the ratio fell to 74 ± 0 49 per cent a significant difference and rose during the afterperiod to 83 6 ± 0 73 per cent revealing an opposite behavior to what was observed in the second experiment * The effect of the high diet upon the plasma proteins was slight and *also different from the previous experiment the total protein increasing* from 6 16 to 6 35 per cent only and the albumin decreasing from 1 15 to 0 73 per cent We shall return to these opposite types of response and attempt partly to correlate them with the different nitrogen balances in the first and second patient

4 The experiment presented in Fig 102 was carried out on a patient with typical nephrosis Mr Edwin T r aged twenty five years At present will be considered the first thirty days of the experiment only The patient was in the comparatively early stage of the disease
worse instead of bette
by the twelfth day o
protein diet From
given calcicum chlor
gastro intestinal upset the high diet was
in Fig 102 From the twentieth to the twenty third day the caloric intake was about 500 daily otherwise 2500 The nitrogen balance during the high diet was definitely positive

The urinary protein during the foreperiod was rather variable in

as follows
e difference
the second

amount increased output in response to the high intake followed by diminished output when the protein intake was reduced is shown in Fig 10? just as in previous experiments The ratio between urinary albumin and globulin in this patient deserves attention While the patient was in the Deaconess Hospital Boston Mass we had opportunity through the courtesy of Dr Howard F Root to examine a sample of his urine It contained a large amount of

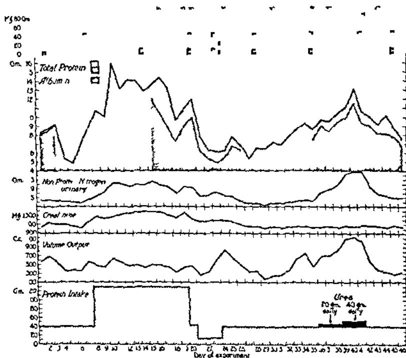


Fig 10? Elimination of urinary protein as influenced by a level of protein intake and (b) ingestion of urea. Discussion on pages 48 and 483 Mr Edwin T r Nephrosis.

stituted 9 , 37 and 100 per cent of the total proteins The urinary proteins were again fractionated when the patient during high protein diet was taking calcium chloride the results were 88 5 and C 3 per cent albumin After discontinuation of the calcium chloride and shift to low diet the albumin gradually increased to

93 2 per cent This cycle in principle corresponded to what was

contributed to the increased loss of globulin That such was not the case may be concluded from observation on Alvin Js, to be

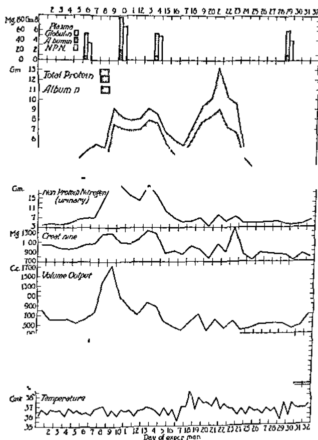


FIG 103 Elimination of urinary protein as influenced by (a) protein metabolism and (b) fever Discussion on pages 484 and 485 Mr Wss Nephrosis

5 Fig

The put to

average above the rate of protein loss during the foreperiod and on discontinuation of the high diet promptly started to decline The urinary albumin during the last days of the foreperiod fell from 9(to 74 per cent of the total protein dropped during the first two days of high diet to (6 per cent then still during the high diet increased to 89 per cent The plasma proteins showed an unusual and transitory increase early during the high diet from 5 32 to 8 75 per cent for the total proteins and from 0 7ɔ to 2 11 per cent for the abumin Once later a similar large increase was observed In Mr Wss there was a combination of high protein diet and rapid loss of edema

The experiments described were carried out on typical instances of nephrosis the patients were sick people with pronounced edema The next 2 experiments are believed to be of value as contrasts to the previous ones They were carried out on 2 patients without any other pathological signs than albuminuria the condition in both instances having been picked up accidentally through routine urine examination During the whole period of the experiments the renal condition showed no signs of change nor were there in either case any signs of active renal irritation The factors entering into the experiments thus seem limited to a chronic condition of

Alvin J s who presented no other abnormal signs than a reversed proportion of albumin and globulin in the plasma and albuminuria without pathological sediment Before the high protein diet the total plasma proteins were fibrinogen 0 4 gm euglobulin loglobulin II 1 gm or total albumin 2 2 gm and total foreperiod on low protein gm ± 0 06 on change to high protein diet it increased after one days lag to 7 12 gm the elevation outlasting the high diet by two days whereupon there was an abrupt return to the level of the foreperiod The mean output for the six days with high proteinuria was 6 46 gm ± 0 18 the output for the seven days following the abrupt drop (fifteenth

eleventh and eighteenth day of the experiment precipitation curves 1 2 and 3 respectively in Fig 105 The albumin on the low diet constituted 96 per cent of the urinary protein fell during the high diet to 80 per cent and on return to low diet likewise returned

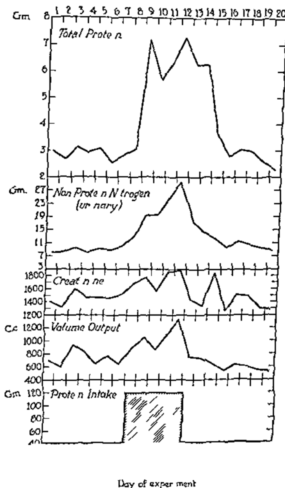


Fig 104 —Relation between protein elimination and level of protein intake Mr Alvin J s Symptom free albuminuria later recognized as chronic Nephritis

to 97 per cent This behavior is identical with what was found to be the case in Experiments 3 to 5 In the present experiment the observations are more detailed and there is in the experiment nothing to suggest anything but a pure physical mechanism nothing indicating aggravation of the renal damage

7 The last experiment in this group was carried out on Mr Laurence R aged thirty-six years in whom symptomless albuminuria was discovered while the patient was being treated for a fresh syphilis at the Boston Dispensary During the long metabol

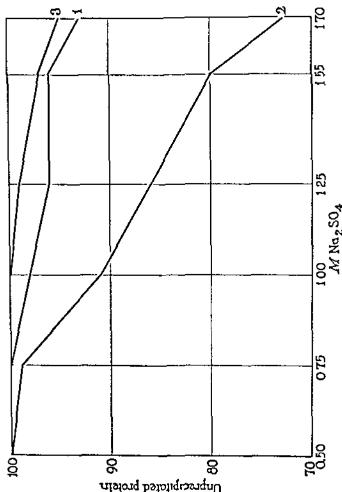


FIG 105 —Precipitation curves for urinary protein from experiment of Fig 104 Curve 1 during preliminary low protein diet curve 2 during high protein diet curve 3 during subsequent low protein diet Mr Al?in J-a

ism experiment different short experiments reported below were run There have been condensed in Table 64 the parts of the high and low protein experiment which with certainty were uninfluenced by the other experiments Table 64 shows the same response as the

preceding experiments an increased protein output on high protein diet and a lesser protein loss upon return to low protein intake The differences between the mean output during the high protein period, 6 93 gm ± 0 25 and during the foreperiod and afterperiod 4 23 gm ± 0 12 and 2 88 gm ± 0 14, respectively, are statistically significant The ratios between the respective differences and their corresponding probable errors are 9 7 and 14 1, respectively

TABLE 64 —SHOWING INCREASED PROTEIN LOSS IN THE URINE ON HIGH PROTEIN DIET

Subject Mr Laurence R l Aged Thirty six Years Diagnosis Syphilitic Nephrosis

Date May July 1925	Condition	Plasma		Urinary protein	
		Total protein per 100 cc gm	Albumin per cent of total protein	Mean 24 hour output gm	Standard deviation (σ)
I Foreperiod *(11 days)*	Diet 40 gm protein *No meat 2500 Cal*	4 96	38 7	4 23 ± *0 12*	0 56
II High protein diet (9 days)	130 gm protein High meat 2500 Cal	6 12 6 90	33 3 30 0	6 93 ± 0 25	1 05
III After period (10 days	Same as *I*	*5 05*	*48 5*	*2 88* ± 0 14	*0 6?*

The ratio between urinary albumin and total urinary protein was frequently determined and varied between 98 and 80 per cent with the mode between 92 and 88 per cent The plasma proteins increased approximately 2 gm per 100 cc on the high diet the increase being greater in the fibrinogen globulin than in the albumin fraction

These constitute our total number of uncomplicated experiments with high and low protein diets in chronic albuminuric conditions That there exists a hematogenous factor in albuminuria as was held before Bright and is held today by Epstein and the investigators who follow him is brought out by these experiments The conditions are decidedly complicated So far we have dealt with the following factors
uz positive or
relative proportio
composition of the plasma itself

PROTEINURIA AND MYXEDEMA

8 *The authors have still* another experiment with high and low protein diets on a patient in whom the condition of heavy albuminuria was complicated by myxedema or *vice versa* The patient,

Mrs A-e , aged fifty-five years, entered the hospital with myxedema, heavy albuminuria slightly decompensated heart and some edema beyond the myxedematous condition The renal condition corresponded well with a nephrosis, the renal function was good, the blood-pressure not elevated The patient had not received thyroid medication prior to the hospitalization While the patient was receiving desiccated thyroid it was noticed that the albuminuria was greatly increased In the meanwhile the metabolic rate had returned toward normal For the sake of the experiment just to be described the thyroid medication was discontinued and the meta-

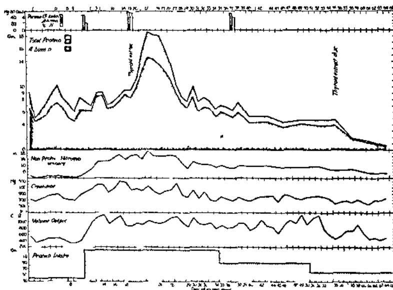


Fig 106 —Elimination of urinary protein as influenced by thyroid administration Mrs A-e Combination of heavy albuminuria and myxedema.

bolic rate was allowed to drop back to −40 The patient was then given meat-free diet containing 40 gm protein and 2000 Calories She was confined to bed Fig 106 and Table 65 reproduce the essential features of the experiment There was during the fore-period a positive nitrogen balance, moderate but definite The response to the high protein diet, calculated to contain 131 gm protein including much meat was prompt as far as the (non-protein) nitrogen elimination went But though this response

the difference lacking statistical significance For the first time we met with a heavy proteinuria which did not respond to increased protein intake with markedly increased proteinuria There was however, another sign of altered protein metabolism, the same as was observed in the first patient, Mr Bsi , who showed a positive nitrogen balance more pronounced than the patient now under discussion This refers to the change in the proportion of albumin in the urinary proteins The authors' first patient Mr Bsi showed a relatively low albumin content on low protein diet, which content increased significantly on high protein diet, simultaneously

TABLE 65 —RELATIONSHIP BETWEEN PROTEIN INTAKE, THYROID FEEDING AND PROTEIN OUTPUT IN MYXEDEMA WITH HEAVY ALBUMINURIA

Mrs A e Aged Fifty-five Years

Condition of experiment	Protein output Mean ± P E	Ratio *	Albumin per cent of total protein Mean ± P E	Ratio *	Nitrogen output (non protein) Mean ± P E	Ratio *
	Gm				Gm	
I Nine days fore-period on 40 gm protein intake	7 92 ± 0 38		76 ± 0 61		2 9 ± 0 12	
II Seven days on high protein diet 130 gm without thyroid medication	8 34 ± 0 28	0 89	91 ± 0 68	16 42	13 3 ± 0 75	13 54
III First ten days of thyroid medication and high protein diet	14 09 ± 0 87	6 29	81 ± 1 14	7 53	16 1 ± 0 45	3 17
IV Six subsequent days conditions same as in III	8 0 ± 0 37	6 42	83 ± 0 69	1 53	10 6 ± 0 48	8 38
V Twenty two subsequent days on thyroid medication but lower protein intake	5 26 ± 0 13	7 04				
VI Nine subsequent days without thyroid medication	1 37 ± 0 10	23 7?				

* Ratio = difference of two means / probable error of the difference

with a heavy increase in proteinuria *All subsequent patients up to the present one had shown the opposite phenomenon a high albumin content on the low diet and a greater proportion of globu* ... nt the albumin ... f the urinary ... ein diet 90 6 ... In harmony with this phenomenon but contrary to what has b n most commonly observed the plasma proteins during the same period showed their greatest increase not in the fibrinogen globulin but in the

albumin fraction the total increase being from 4 92 to 5 7 gm per 100 cc of which the albumin constituted 19 1 and 31 per cent

low diet never fully to return to the high values immediately before the thyroid medication The urinary (non protein) nitrogen during the same period of high protein elimination likewise showed an increase but less marked than the protein

Under continued thyroid medication the protein intake was reduced first to 90 gm and sixteen days later to 60 gm daily During this time there was a gradual drop in the urinary proteins to between 4 and 5 gm daily During this time the albumin fluctuated between 80 and 89 per cent of the total protein When after thirty-six days of thyroid medication its administration was discontinued the urinary proteins promptly fell from between 4 and

was started Less than one month after the end of the experiment the urine became free of albumin and remained so for the subsequent four years The thyroid medication was resumed shortly

substance to myxedematous and normal individuals (Magnus-Levy Grafe Boothby and collaborators) Of interest from the point of view of the present experiment is Boothby s interpretation of this phenomenon as due to a mobilization of reserve protein particularly the amount contained in the myxedema In the case of Mrs Ve we failed to obtain an unquestionably significant increase in the urinary (non protein) nitrogen following the administration of desiccated thyroid but obtained a highly significant

leaking large amounts of protein escaped through the kidneys before deamination could occur On this point one recalls Thompson s demonstration of increased plasma volume immediately following

substitution therapy in myxedema In the *subject of Experiment 6*, Alvin J s, desiccated thyroid was administered but failed to increase the protein elimination

MISCELLANEOUS INFLUENCES UPON PROTEINURIA

The experiments so far presented have dealt with the hematogen ous factor in proteinuria Next will briefly be described a motly variety *of short experiments* some *elucidating* the nephrogenous or renal factor, others leaving us without possibility to decide between one or the other Most of these experiments were done early during this work with the purpose of ascertaining and eliminat ing the factors which were most apt to interfere with the metabolic *experiments The experiments deal with the effects of diuresis* as studied by the dilution concentration test, of posture, of sodium chloride, of calcium chloride given to produce an acid and sodium citrate to produce an alkaline urine, of urea, of injection of arsphen-amine, of blood transfusion and of fever

Cushny s review of albuminuria[20] *brings out how scanty is the* knowledge of the factors which influence its amount and composi-tion The view first advanced by Runeberg,[66a] a Finnish clinician and supported by Cushny, of the glomerular structure as responsible

is based as much upon
ion as upon histological
glomerular capsule

Table 66 shows in some detail the behavior of urinary protein during a dilution-concentration test on Mr Laurence R, *the subject* in Experiment 7 When this test was run the patient was on low protein intake During two hours from 8 to 10 A M the specific gravity fell from 1 030 to 1 001 the diuresis increased from a rate of 16 5 to 335 cc per hour and the protein concentration fell from *710 to 31* mg per *100* cc *urine In another hour s time from* 10 to 11 A M the specific gravity climbed to 1 014, the diuresis fell from 335 to 43 cc per hour and the protein concentration rose from 31 to 247 mg per 100 cc urine With these extensive variations in the composition of the urine the protein output per hour remained *practically as* constant as the creatinine output the latter varying ±8 per cent and the former +17 and −10 per cent from the output of the two hour foreperiod between 6 and 8 A M From 9 A M to 12 NOON, during which time the *composition of the urine changed* considerably, there was no variation either in protein or in creatinine elimination

The experiment conclusively shows the rate of protein elimination to be independent of the concentration of the urine of the rate of *diuresis and of the* urinary protein concentration Incidentally it demonstrates the futility of estimating, quantitatively or semi-

quantitatively the amount of albumin in a urine sample without taking into account specific gravity or diuresis

TABLE 66 DILUTION-CONCENTRATION TEST SHOWING THE ALBUMIN OUTPUT TO BE INDEPENDENT OF THE DIURESIS

Subject Mr Lawrence R-l Aged Thirty-six Years Diagnosis Albuminuria in Syphilis

Time 19 5	Condition	Urine							
		Amount cc	Specific gravity	Protein per 100 cc mg	Protein per hour mg	Protein per 24 hours gm	Albumin per cent of total	Creatinine per hour mg	Creatinine per 24 hrs mg
June 7	Low protein diet	365				*3 78*	88 0		1105
8		380	1025			*4 00*	94 7		1170
9									
6 8 A M	8 A M 1000 cc water by mouth on empty stomach	33	1030	710	*117*		88 0	50	
9 A M		112	1006	1	*19*		91 0	54	
10 A M		335	1001	31	*105*		85 4	46	
11 A M		74	1007	143	*106*		93 8	46	
1 NOON	Dry luncheon	43	1014	4	*106*		87 0	45	
3 P M		14[illegible]	101	76	*12[illegible]*		9 9	49	
6 P M	From 6 P M free fluid intake	108	1020	445	*161*		8 6	45	
7 A M		168	10[illegible]4	67	*94*	*[illegible] 79*	84 0	44	1143
June 10		365	1034			*4 53*	84 3		1150
11		365	1035			*4 50*	89 0		1150

For the creatinine the accepted interpretation of its constancy is a constant production of excretable creatinine as far as this experiment goes [41]

a con

under

discussion This would mean that the experiment forms a counterpiece to the straight line filtration curves given by Medes and Berglund as Fig 43 in their paper on Rehberg s test (page 217) Such is the authors interpretation of the experiment

Another dilution-concentration test on the same patient while on high protein diet Table 67 is interpreted in light of the curves of el mma fl

between 8 and 9 A M as the first effect of the ingested water in opening up a greater number of glomerular capillaries The same effect was noticeable in Table 66, where the urine secreted between 8 and 9 A M carried with it a slightly increased amount of protein Returning to Table 67, there was a gradual drop in protein excretion from 9 A M during the remainder of the forenoon, just as in the curves on page 493

TABLE 67—DILUTION CONCENTRATION TEST SHOWING PROTEIN ELIMINATION TEMPORARILY INCREASED COINCIDENT WITH ONSET OF DIURESIS BUT INDEPENDENT OF THE HEIGHT OF THE DIURESIS

Subject Mr Laurence R-l Aged Thirty six Years. Diagnosis Albuminuria in Syphilis

Time 1925	Condition	Urine						
		Amount cc	Specific gravity	Protein per 100 cc mg	Protein per hour mg	Protein per 24 hrs gm	Creatinine per hour mg	Creatinine per 24 hrs mg
June *27*	High protein diet with meat	890	1027			*5 70*		1390
28		780	1026			*6 90*		1335
29								
6–8 A M	8 A M 1000 cc water by mouth on empty stomach	56	1025	599	*168*		55	
9 A M		108	1008	208	*224*		57	
10 A M		335	1005	46	*155*		54	
11 A M		62	1010	209	*129*		54	
12 NOON	Dry luncheon	54	1012	205	*111*		55	
3 P M		105	10?1	382	*134*		57	
6 P M	From 6 P M free fluid intake	112	1024	453	*169*		62	
7 A M		410	10?5	438	*138*	*3 66*	55	*1408*
June *30*		830	1025			*6 94*		1372
July *1*		875	1032			*9 95*		1421

t is carried out on Mr Bsı,
It should be recalled that the
diuresis resulting from the
the edema free
ingestion of 1 and
Mr R l the oon
to 172 cc in ıfter
The 54-cc ur
the drinking of the water showed the maximum proteinuria, 251 mg, as *versus* 194 mg during the preceding and 200 mg during the fol-

lowing hour The creatinine output was constant to the milligrams from hour to hour

These experiments are presented as examples of the renal factor in proteinuria

It will be noticed that in both Tables 66 and 67 the day of the water test showed a twenty-four-hour protein output significantly lower than the respective averages The same was the situation in Mr Bst For this phenomenon no explanation can be offered The total caloric intake during the days of the test was divided between two meals instead of three On the strength of these observations, and since the metabolism experiments were run on patients without renal insufficiency, we have made it a rule to keep the urinary volume nearly constant by restricting the fluid intake

TABLE 68 — SHOWING THE EFFECT OF BODILY POSITION AND ACTIVITY ON THE ELIMINATION OF URINARY PROTEINS

Subject Mr Laurence R-l Aged Thirty-six Years Diagnosis Albuminuria in Syphilis

Time 1925	Condition	Urine				
		Amount cc	Protein per hour mg	Protein per 24 hours gm	Creatinine per hour mg	Creatinine per 24 hours mg
May *19*						
7 9 A M	In bed all day	-9	59		50	
9–11 A M		32	66		72	
11 1 P M		37	74		56	
1 P M 7 A M		345	102	2 23	54	1328
May *21*						
7 9 A M	Out of bed and actively walking about from *9 to 10 30 A M*	74	124		64	
9 11 A M		65	236		59	
11 1 P M		122	133		53	
1 P M 7 A M		285	137	3 45	49	1-31
June *10*		365		4 31		1150
11		365		4 50		1150
1•		3`0		3 36		10`0
13	Out of bed walking all day	610		8 05		1220
14		450		5 84		1175
15		380		2 65		1060
16		330		1 38		1040
17		645		2 36		10"1

unchanged protein output while out of bed for two days With these experiments excepted during all our observations the patients have been confined to bed

TABLE 69 —SHOWING TEMPORARY DEPRESSION OF URINARY PROTEINS FOLLOWING ADMINISTRATION OF SODIUM CITRATE

Subject Mrs Bs Aged Forty-three Years Diagnosis Chronic Nephrosis

Time 1925	Condition	Body weight kg	Urine		
			Amount cc	Protein per 24 hrs gm	Creatinine per 24 hrs mg
June 10	Low protein diet	63 0	575	7 00	695
11			850	10 08	800
12			690	7 90	800
13			1035	6 16	850
14	Sodium citrate 20 gm	63 0	660	2 95	755
15	Sodium citrate 20 gm	64 0	545	6 61	[illegible]5
16		63 8			
17			880	8 68	[illegible]05
18		65 0	720	7 23	7[illegible]6

TABLE 70 —SHOWING THE INFLUENCE OF ALKALI UPON PROTEIN ELIMINATION

Subject Mr Laurence R l Aged Thirty six Years Diagnosis Albuminuria in Syphilis

Time 1925	Condition	Body weight kg	Urine		
			Amount cc	Protein per 24 hrs gm	Creatinine per 24 hrs mg
June 2	Low protein diet		1[illegible]35	3 86	1 35
3		56 0	[illegible]75	3 91	1[illegible]40
4	Sodium citrate [illegible]0 gm		465	2 [illegible]1	1180
5			435	3 10	1[illegible]40
6			355	3 28	1190
7		54 0	365	3 78	1105
July 6	High protein diet		845	9 88	1535
7			865	6 85	1559
8	Sodium citrate 20 gm	54 6	1065	4 67	15
9	Sodium citrate 20 gm		945	5 30	14[illegible]
10			825	12 40	14[illegible]
11			800	5 13	1360
12		54 6	815	6 14	1595

intake was not increased

Opportunity to observe the effect of fever or of infection upon proteinuria offered itself in Mr W–s (Fig 101) who on the fourth day after the discontinuation of the high protein diet developed an acute infection of the remaining lymphatic tissue of the throat The temperature (oral) rose to 38 5° C was on the second day 37 9° C on the fourth day 37 8° C on the fifth or sixth day back to normal Increased protein output accompanied the infection, surpassed the proteinuria of the preceding high diet and reached

13 3 gm the fourth and last day of the fever, whereupon it fell *abruptly to a slightly lower level than before the high protein diet* The albumin fraction of the urine fell during the fever from 85 to 65 per cent at the height of the protein output, again to return to 80 and 85 The creatinine elimination showed a sharp peak with the return of normal temperature

This observation lends assurance to the interpretation of the last part of Fig 100 picturing the second experiment on Mr Bsi On the thirty first day of that experiment the patient s temperature rose to 99 6° F there was pain in the left side of the chest with a friction rub Simultaneously with this evidence of infection the protein elimination rose abruptly, reaching 17 3 gm on the second day the pleural irritation subsided the temperature was normal again the second day and remained so and the protein output started on a downward course

After the protein output on the thirty-eighth day had come down to 10 14 gm a blood transfusion was given on the thirty-ninth day *of the experiment Citrated blood was transfused, 450 cc contain* ing 250 cc plasma of a protein content of 7 65 per cent and a ratio of albumin to globulin of 1 35 to 1 The recipient s plasma before the transfusion contained 5 9 per cent protein with a ratio of albu min to globulin of 1 to 2 11 Immediately after the transfusion the plasma concentration was 5 63 per cent and the ratio of albumin to globulin was determined as 1 to 1 98 There was no transfusion reaction The urinary proteins the day of the transfusion were increased to 15 9 gm and the *following day to 13 85* gm whereupon the downward course of the proteinuria was resumed

... increased proteinuria in fever ... enous ... *other*

STUDY OF PLASMA AND URINARY PROTEIN FRACTIONS

Though the different proteins which make up the plasma have long been studied and their individuality recognized—years ago ... ndent behavior

and the albumin have been dist gu ...
than by their biological response

When on the following pages we speak of fibrinogen, euglobulin

* It is outside the scope of this report to enter into a d scuss on of the chemistry of the plasma prote ns Among several valuable discussions of this topic the following are called to the reader s attention Sørensen S P L Proteins lectures given in the United States of America in 1924 The Fleischmann Laboratories 1925 l mited ed tion Hynd Lancet ii 910 1925 Hewitt Biochem J 21 216 1927 Cavett and Gibson J Clin Invest 10 857 1931 Widdowson B ochem *J* 27 *1321 1933*

pseudoglobulin I, pseudoglobulin II and albumin we do so for the sake of convenience to save the reader from the descriptive expressions the protein fraction precipitated between sodium sulphate concentrations of 0 5 and 0 75 M (fibrinogen) of 0 75 and 1 M

authors graphic presentations they retain the expression of the molarity of the precipitant instead of the conventional names The textbooks of biochemistry inform us that the different fractions may be separated and characterized by other means than by their solubility in sulphate solutions In the separation by the salting-out process which we have used the fact should be called attention to that in normal plasma the precipitation from 0 5 to about 1 4 or 1 45 M Na_2SO_4 is continuous without any neutral zones and that it is only between approximately 1 45 and 1 55 M that no precipitation takes place Thus it is only in the separation of the

bility described above which has not been checked as fibrinogen, for instance by determination as fibrin The fact that *normal* fibrinogen values obtained by both methods check completely gives slight guarantee that the same holds for pathological material though fibrinogen concentrations at least three times normal have been determined as fibrin (Gram[34]) The fibrin method on the other hand might under circumstances give too low values

Whatever the chemical individuality of the protein fractions may be as the salting-out method now stands with the conditions under which the precipitation takes place properly worked out the method affords a mean of an objective and quantitative description and characterization in regard to solubility of plasma and urinary proteins As such the authors have used it

The common knowledge about the functional behavior of the plasma proteins consists of a few facts for instance that the fibrinogen globulin fraction is increased in animals used for the production of specific immune bodies during pregnancy and in patients afflicted with kala-azar and leprosy and that the albumin fraction may be greatly reduced in nephrosis and nephritis The authors have twice observed instances where the albumin was *reduced to 0 25 per cent and the reader's attention may already here be called to the massive increase in the fibrinogen-euglobulin content depicted in Fig 111 (page 535) The existence of an enormous capacity to synthesize plasma proteins must be concluded

from the necessity of large and frequent plasmapheresis in order to maintain hypoproteinemia *in dogs* On shifting a dog (recovering from uranium poisoning) from low to high protein diet the authors observed *a change* in plasma protein concentration from 5 31 to 8 27 per cent *in five days* *In this* particular instance the increase was about equally divided between the albumin and globulin fractions, prompting the question *to what extent* the change in concentration was due to dehydration or to synthesis of new proteins *This problem usually does not enter in, as exemplified in* Mr *W-s* (Fig 103) in whom on change from low to high protein diet within *four days the* plasma proteins rose from 5 32 to 8 75 gm per 100 cc, with the albumin fraction going from 14 to 28 per *cent* *In a more* recent observation in a patient (Malberg) convalescing from acute nephritis with colossal edema the total proteins rose from 5 36 *to* 7 02 per cent and the albumin from 0 42 to 2 3 per cent or more *than the total* increase, indicating a complete change of pattern Equally striking changes in opposite direction within very short time are also observed, as in a patient (E-v-f) with chronic nephrosis edema-free and in full activity on high protein diet This patient had 6 59 per cent protein in his plasma of which 2 16 per *cent was albumin* *After four days on low protein diet his total* [illegible]

rather than the average run have been chosen in order to engage the reader s interest in the following statistical study of the plasma and urinary proteins

TABLE 71 COMPOSITION OF NORMAL PLASMA PROTEINS

Protein	Mean ± P E	Standard deviation (σ) ± P E σ	Coefficient of variation
Fibrinogen	0 294 ± 0 010	0 06[illegible] ± 0 007	21 0
Euglobulin	0 681 ± 0 06[illegible]	0 389 ± 0 044	57 1
Fibrinogen and euglobulin	0 974 ± 0 065	0 407 ± 0 046	41 8
Pseudoglobulin I	0 939 ± 0 049	0 306 ± 0 034	3[illegible] 5
[illegible]	0 681 ± 0 041	0 25[illegible] ± 0 0[illegible]9	37 9
[illegible]	[illegible]	[illegible] ± 0 030	17 2
[illegible]	[illegible]	[illegible] ± 0 040	12 9
[illegible]	[illegible]	[illegible] ± 0 050	11 4
[illegible]	[illegible]	[illegible] ± 0 070	8 7

Values representative of normal concentration and normal variability of plasma proteins are presented in Table 71 The material consists of determinations in 19 normal individuals physicians and assistants around the laboratory The mean total protein concentration was 6 60 per cent ± 0 09, the albumin was 4 07 per cent ±

0.07 and the fibrinogen globulin fraction 2.59 per cent ± 0.05 These values are identical with the means obtained by Linder, Lundsgaard and Van Slyke from eight determinations on 7 individuals

and coefficient of variation for each group

Table 72 contains corresponding information about pathological plasma Table 72 is based upon 8[illegible] plasmas from practically the same number of patients predominantly afflicted with renal disease some with diseases of heart liver blood or bone-marrow No patients with kala azar leprosy acute pneumonia or acute yellow atrophy are found among our material

TABLE 72 COMPOSITION OF PATHOLOGICAL PLASMA PROTEINS

Protein	Mean ± 1 E	σ ± 1 E	Coefficient of variation
Fibrinogen	0 [illegible]47 ± 0 0[illegible]	0 [illegible] ± 0 010	10[illegible] 0
Euglobulin	0 [illegible] ± 0 0[illegible]5	1 0[illegible]0 ± 0 0[illegible]	1[illegible] 0
Fibrinogen and euglobulin	1 [illegible] ± 0 1[illegible]0	[illegible] ± 0 0[illegible]	101 0
Pseudoglobulin I	1 130 ± 0 0[illegible]	0 4[illegible] ± 0 0[illegible]	3[illegible] 8
Pseudoglobulin II	0 774 ± 0 0[illegible]	0 [illegible] ± 0 015	3[illegible] 5
Pseudoglobulin I and II	1 900 ± 0 040	0 50[illegible] ± 0 0[illegible]	[illegible]
Total globulin including fibrinogen	3 4[illegible]0 ± 0 110	1 560 ± 0 0[illegible]0	41 9
Albumin	2 960 ± 0 080	1 [illegible]0 ± 0 0[illegible]0	38 9
Total protein	6 430 ± 0 120	[illegible] ± 0 0[illegible]0	[illegible]

The mean total protein was 6.43 per cent ± 0.12 which figure does not vary significantly from the normal mean the ratio of the difference to the probable error of the difference being = [illegible] The standard deviation and the coefficient of variation for the pathological [illegible]

While the albumin showed diminution, the total globulin, including

larger than for the normal

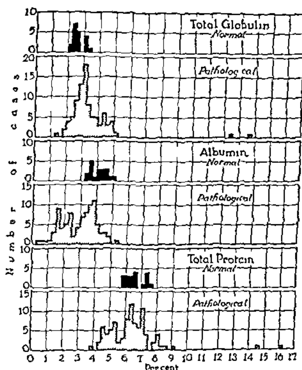


FIG 107 — Distribution of normal and pathological plasma protein values

of the difference and the probable errors of the difference being 3 3 To ... the pathological plasmas are significantly

nt The

Fig 108 —Distribution of normal and pathological plasma protein values.

pathological albumin For this fraction the material did not prove homogeneous showing two groups of slightly different size one approximately of normal values the other with lower values No such cleavage is present in the other fractions from the same plasmas The group with the lower

While the albumin showed diminution the total globulin including fibrinogen showed significant increase the mean being 3 47 per cent ± 0 11 as *versus* the normal 2 59 ± 0 05 The difference is significant the ratio of the difference to the probable error of the difference being 7 3 The coefficient of variation for the pathological group is more than three times larger than for the normal

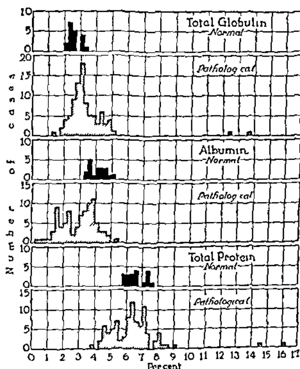


FIG 107 —Distribution of normal and pathological plasma protein values

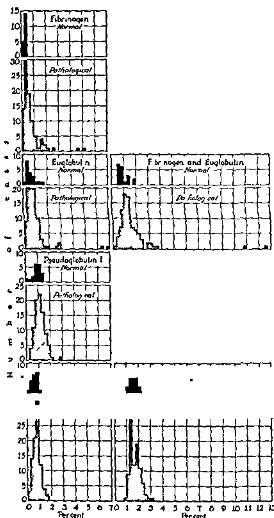


FIG 108 —Distribution of normal and pathological plasma protein values

While the albumin showed diminution, the total globulin, including fibrinogen showed significant increase the mean being 3 47 per cent ± 0 11 as *versus* the normal 2 59 ± 0 05 The difference is significant the ratio of the difference to the probable error of the difference being 7 3 The coefficient of variation for the pathological group is more than three times larger than for the normal

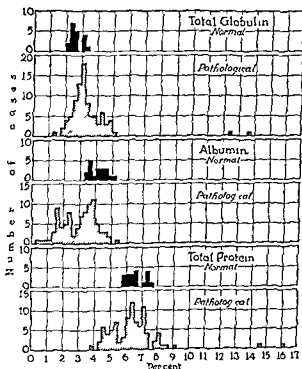


FIG 107 — Distribution of normal and pathological plasma protein values

f th d ff rence be ng 3 3 To-

gen and albumin vary usually in opposite directions The authors material both in this and subsequent chapters in regard to these two large fractions amply demonstrates an independent variation the euglobulin fibrinogen fraction frequently being increased independently of any alteration of albumin The reader will have noticed that the authors have refrained from the use of the term

nephrosis As an instance of proteinuria in renal insufficiency with uremia they offer the findings in a young man from the Peter Bent Brigham Hospital (Med No 25816) James R y whom they studied in some detail during the last fifteen days of his life

albumin

In toxemia and eclampsia of pregnancy on urines obtained from the

failure The following observation may be cited as an instance where

The low albumin with rare exceptions is due to an extraneous process heavy renal leakage but not a part of the other intrinsic plasma changes

The euglobulin and fibrinogen present a different situation *Fig 108* reveals a marked skewness in the distribution of the observations this is true al o for the normal euglobulin The pathological means 0 747 per cent ± 0 057 for fibrinogen and 0 874 ± 0 075 for euglobulin both show standard deviations larger than the normal and correspondingly high coefficients of variation 107 for fibrinogen and 120 for euglobulin Both means were higher than the normal means A more adequate presentation of these values is given by Table 73 comparing the normal and pathological

TABLE 73 DISTRIBUTION OF FIBRINOGEN AND EUGLOBULIN VALUES IN NORMAL AND PATHOLOGICAL PLASMA ACCORDING TO QUARTILES THE VALUES REPRESENT GRAMS PROTEIN PER 100 CC PLASMA

	Min	25 per cent	50 per cent	75 per cent	Max
Fibrinogen					
Normal	0 16	0 25	0 29	0 3?	0 40
Pathological	*0 03*	*0 19*	*0 39*	*0 7?*	*5 19*
Euglobulin					
Normal	0 20	0 37	0 51	0 78	1 64
Pathological	0 13	0 28	0 56	0 85	7 41

The fact that the total protein both normally and pathologically shows lower [illegible]
sarily brings [illegible]
in a reciproca[illegible]
be the case with the two pseudoglobulins For the other fractions we believe the question is to be answered in the negative The relative constancy of the total protein depends on the fact that around the highly constant pseudoglobulins the euglobulin fibrino-

gen and albumin vary usually in opposite directions The authors' material both in this and subsequent chapters in regard to these two large fractions amply demonstrates an independent variation, the euglobulin fibrinogen fraction frequently being increased independently of any alteration of albumin The reader will have noticed that the authors have refrained from the use of the term

nephrosis As an instance of proteinuria in renal insufficiency with uremia they offer the findings in a young man from the Peter Bent Brigham Hospital (Med No 25810), James R-y , whom they studied in some detail during the last fifteen days of his life

albumin

The authors have not extensively studied proteinuria due to heart failure The following observation may be cited as an instance

The material in preceding sections showed great variability in the relative amounts of album n and glob [illegible]

In the uremic patient just described no such experiment could be carried out In patient Grace C-n , discussed in next section and in Table 76, with definitely reduced renal function, the level of protein metabolism was varied greatly, this was followed by corresponding changes in protein elimination but the globulin fraction varied two-sixths only from its maximum relative amount Other observations pointing in same direction support the conclusion that in renal insufficiency the variability of the protein composition of the urine is less than when renal function is preserved

TABLE 74 —COMPARISON OF THE SOLUBILITY OF URINARY PROTEIN NORMAL PLASMA PROTEIN AND PATHOLOGICAL PLASMA PROTEIN IN TERMS OF PERCENTAGE UNPRECIPITATED PROTEIN AT DIFFERENT CONCENTRATIONS OF SODIUM SULPHATE THE PLASMA FIGURES ARE CALCULATED FROM TABLES 69 AND 70

M concentration Na_2SO_4	Urine		Plasma	
	Mean ± P E	σ ± P E	Normal	Pathological
0 75	97 9 ± 0 33	2 78 ± 0 23	95 6	88 4
1 00	*94 3 ± 0 73*	*6 09 ± 0 51*	*85 4*	*74 8*
1 25	84 9 ± 1 46	12 23 ± 1 03	71 3	57 3
1 55	76 5 ± 1 62	14 80 ± 1 14	61 0	45 3
1 70	75 4 ± 1 9?	12 06 ± 1 36	55 5	35 1

Three precipitation curves for urinary proteins from 1 individual were given in Fig 105 In Table 74 are given the mean values and standard deviations for 38 different curves, 19 of which also included precipitation with 1 7 M Na_2SO_4 The curves were obtained from 23 individuals with different types of renal disease It is evidently impractical with urinary protein of widely different concentrations to use absolute values for means or curves The values of the different fractions instead are expressed in percentage of total protein Table 74 gives in percentage of the total protein the amount still unprecipitated at each concentration of sodium sulphate [illegible] f the [illegible] prote ns with the normal [illegible] of the plasmas [illegible] same manner and included in Table 74 in its last two columns Inspection of the individual cases in which plasma and urine were studied con-

[illegible] is given in Fig 109

After the previous discussion of the variability in composition of urinary protein it is worth realizing that a general pattern may nevertheless be recognized, sufficiently characteristic to be compared with the corresponding pattern of the blood On comparison one finds the standard deviations of the urinary fractions to be of the same order of magnitude as those of the blood fractions The coefficients of variation if calculated not for the unprecipitated protein, but for the precipitated amounts at each salt concentration, range much as in the plasma from about 130 for fibrinogen step by step down to 50

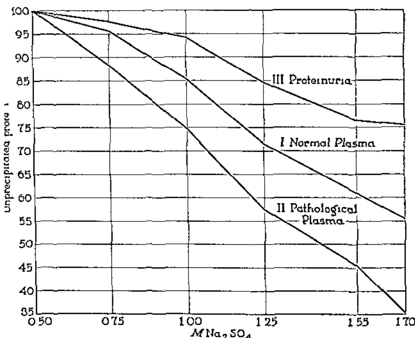


FIG 109 —Comparison of precipitation curves for urinary proteins normal plasma proteins and pathological plasma proteins

Attempting to express what the difference between the urine

the difference between the proteinuria curve and the pathological

plasma curve means that in equal amounts of urinary and plasma proteins 1 mg of each fraction of the former will be represented by the following number of milligrams of the same fraction in the latter Fibrinogen 1 to 5 5 eugl
1 to 1 9 pseudoglobulin II 1 to
one might say that albumin will
proximately ten times easier than fibrinogen (or a plasma protein of the solubility of normal fibrinogen) and so on The composition of urinary protein usually might have little to do with the alteration of the filtering membrane or with the magnitude of the plasma fractions it is more closely dependent upon physical properties of the plasma proteins such as molecular weight viscosity or other factors One possible exception exists namely amyloidosis In 1 subject this diagnosis was made the ratio between urinary and plasma protein came out as follows fraction by fraction Fibrinogen 1 to 1 2 euglobulin 1 to 0 8 pseudoglobulin I 1 to 1 5 pseudoglobulin II 1 to 1 1 and albumin 1 to 0 8

One type of curve frequently observed in nephrosis or long standing nephritis shall be mentioned The curve first runs almost flat with a sudden drop in the area of pseudoglobulin I (M 1 to 1 25) whereafter nothing more comes down within the range of
... running absolutely horizontal even
on
the three curves of Fig 109 in this area deserves comment the urinary protein curve running almost horizontally the pathological plasma curve being the steepest the normal plasma falling between It seemed important to prove that these differences are statistically significant The means of the amounts precipitated between 1 55 and 1 7 M salt concentration from normal and pathological plasmas were 363 mg ± 26 and
... ratio between the difference of
the difference was 5 1 Since
the plasma curves thus meets
... difference in

A PROTEIN CREATININE TEST FOR GLOMERULAR PROTEIN LEAKAGE

It is not known how to correlate albuminuria with other phenomena intrinsic with a diseased kidney It is not likely that a morbid sign as prominent as albuminuria cannot in some way be correlated with reduced renal function Surely in essential hypertension albuminuria occurs or increases with deterioration of function Generally it might be stated that though heavy albu

minuria may or may not be present from a diseased kidney with preserved function, there is no renal insufficiency without marked albuminuria This statement should be guarded by confining it to renal insufficiency of glomerular or vascular origin, though the majority of instances of renal insufficiency has this pathogenesis, there are at least two groups of exceptions and the authors have observed instances of both (1) Renal insufficiency in myeloma and Bence-Jones proteinuria without albuminuria, and (2) renal insufficiency in hydronephrosis and increased back pressure in prostatic hypertrophy Since as it has been shown in Tables 66 and 67 (pages 493 and 494), the concentration of urinary protein has to be correlated with the rate of diuresis or rather with the degree of concentration of the urine equally heavy albuminuria should not be expected in isosthenuria as in a highly concentrated urine This expectation, reasonable as it may appear, needs to be tested because of the singular position occupied by proteinuria While other compounds are being retained proteins are being spilled Rowntree and Geraughty were uncertain which would be the fate of phenolsulphonephthalein whether it was going to leak through the diseased kidney in increased amount like protein or be retained like urea

We know that proteinuria cannot be correlated with the protein concentration of the plasma nor even with its content of albumin, though it is closely correlated with the protein intake We also know that the hourly protein elimination may be as constant as the creatinine output and independent of diuresis The authors have concluded that the protein leakage takes place in the glomeruli a conclusion supported by Bieter s observation [7] that proteinuria cannot be produced in the aglomerular kidney Thus it becomes natural to attempt a correlation of proteinuria with glomerular function This may be done by the use of the rate of glomerular filtration determined according to Rehberg It is plausible that with most glomeruli functioning more protein might be lost than if 70 to 80 per cent of the filtering structures have been wiped out The authors have determined the amount of protein in the urine sample of the Rehberg test They have attempted to correlate the one hour protein elimination with the rate of glomerular filtration and found no correlation Such a correlation would have indicated a somewhat identical degree of glomerular leakage in all diseased kidneys The authors have further calculated the concentration of the eliminated protein in the glomerular filtrate in the following way In Rehberg s creatinine test one arrives at the minute filtration from the concentration index for creatinine and the volume of urine They arrive at the intracapsular concentration of the protein from the amount of urinary protein and the volume of glomerular filtrate, simultaneously determined by the creatinine test, or, more simply,

from the concentration of the urinary protein and the concentration index of the creatinine

TABLE 75 —PROTEIN LEAKAGE IN GLOMERULAR FILTRATE CALCULATED FROM THE PROTEIN-CREATININE TEST

No	Filtration rate cc per min	Urine volume cc per hr	Protein concentration mg per 100 cc	Protein elimination mg per hr	Protein in glomerular filtrate mg per 100 cc	Albumin per cent of total protein	Creatinine excretion mg per hr	Concentration ratio for creatinine
1	260	200	32	64	0 4		642	78
2	169	47	416	196	1 9	75 2	329	216
3	143	45	195	89	1 0	86 2	412	160
4	140	140	159	223	2 7		280	53
5	139	190	68	129	1 6		399	44
6	132	45	825	372	4 7	85 2	257	177
7	121	285	24	68	0 9		578	26
8	114	17	3516	598	8 8	83 0	323	402
9	111	96	422	405	6 1	77 2	376	70
10	109	14	4078	571	8 8	83 0	302	466
11	108	81	384	311	4 8	65 1	360	80
12	94	40	518	207	3 7	69 5	190	141
13	88	164	469	769	14 6		505	32
14	85	112	24	27	0 6	61 8	196	46
15	49	97	260	252	8 6	65 6	215	30
16	48	175	453	793	27 6	68 7	273	16
17	31	55	500	275	14 8		51	34
18	26	55	1050	578	37 2	63 8	121	28
19	24	195	379	739	51 7		140	7
20	23	217	270	586	41 9	74 8	156	7
21	23	38	1875	713	51 0	65 2	82	37
22	22	26	1246	561	23 8		88	52
23	19	216	272	588	52 1	60 3	112	5
24	18	76	197	150	13 8		112	14
25	10	100	195	195	33 1	66 7	86	6
26	7	46	551	254	59 4		44	9
27	6	88	97	85	25 5		57	4
28	4	35	197	70	28 6		34	7
Additional								
29	6	37	954	359	100 0		39	10
30	6	52	319	166	49 8		49	6
31	132	37	326	121	1 5		277	215
32	7	97	553	536	106 0		63	4
33	36	54	578	312	14 4		170	40
34	98	22	117	26	0 9		354	264
35	20	30	1659	498	42 3		80	39
36	78	290	34	99	2 1	76 0	350	16
37	77	96	98	94	2 0	98 5	160	48

The results of 28 such protein-creatinine tests are compiled in some detail in Table 75 The material shows a wide spread with filtration-rates from 260 to 4 cc per minute, only one big hole

occurring with no rates between 85 and 49 cc Eleven of the 28 observations had filtration rates above 100 cc and 12 below 40 cc The one hour urinary volume varied between 285 and 14 cc the protein concentration between 40 8 and 24 mg per 100 cc and the protein output between 793 and 27 mg per hour urine calculation of the protein concentration in the glomerular filtrate renders values between 0 4 and 59 4 mg protein per 100 cc Six of the 28 observations gave values lower than 2 mg per 100 cc and 11 gave values above 20 mg There exists a marked negative

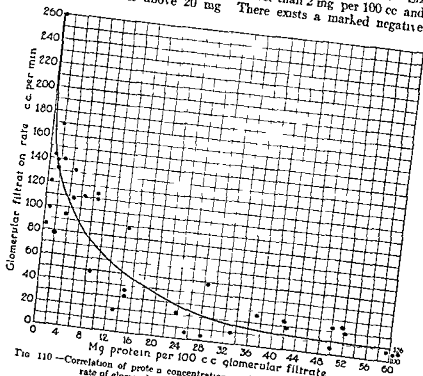


Fig 110 —Correlation of protein concentration in the glomerular filtrate against rate of glomerular filtration Protein-creatinine test

correlation between protein concentration and filtration rate as demonstrated by Fig 110 * Thus as large numbers of renal units cease to function the remaining filtering units become altered in such a way that they allow protein to pass in increased concentration The absolute figures obtained by this calculation are surprisingly low lower than the protein concentration in edema fluids for which particularly when edema is increasing one might assume

* A few more observations have been appended to Table 75 and also laid in on Fig 110 They confirm the findings in the 75 first tests.

very slight or no concentration of the transudating fluid to take place. The figures resemble the protein content of cerebrospinal fluid.

Observations 8, 10 and 21 in Table 75 were made on the same patient [illegible]

filtrate from 8.8 to 51 mg per 100 cc.

This might be written

$$\frac{P_u}{t} \times \frac{V}{F} \times 100 = P_r$$

where P_u = urinary protein in mg per 100 cc
t = time of experiment (60 minutes)
V = urinary volume
F = glomerular filtrate cc per minute
P_r = protein mg per 100 cc of glomerular filtrate

Or more simply

$$\frac{P_u}{\frac{C_u}{C_B}} = P_r$$

[illegible]

[illegible] that

$$F = \frac{\ }{C_B} \times \frac{\ }{t}$$ (Rehberg's equation)

In the accompanying figure we have plotted F (ordinate) against P_r [illegible]

$$F = (f)\, P_r$$

may also be written

$$\frac{C_u}{C_B} \times \frac{V}{t} = (f)\, \frac{P_u}{\frac{C_u}{C_B}}$$

in which the term $\left(\frac{C_u}{C_B}\right)$ appears on both sides of the equation once in the [illegible]

determine quantitatively.

This behavior in proteinuria, increasing permeability to protein with decreasing amount of functioning renal tissue, we have been tempted to interpret as the most important renal factor in proteinuria. How is this factor influenced by the various hematogenous factors? Some observations are presented on the effects of the

most important of these factors, the level of the protein intake Miss Grace C-n (Table 76), with chronic nephritis and secondary hypertension of two years' duration, during the first year presenting marked and persistent edema, during the second year in good general condition, in the course of nine days was submitted to four protein-creatinine tests on high and low protein diets, and again on high protein diet Table 76 also includes an earlier test on high protein diet twenty days prior to the first test of the series Table 76 [illegible]

concentration in the glomerular filtrate show very large variations, the minute filtration four and a half times its lowest value and the protein concentration a little more than three times From the table is clearly illustrated that variations in filtration-rate influence the value for the protein concentration in the filtrate to a greater extent than variations in the hourly protein output or in the level of protein intake This fact ordinarily is somewhat hidden by the mode of expression filtration-rate being given per minute and protein output per sixty minutes The authors believe that the long metabolism experiments which constitute the first part of this treatise may be advantageously replaced by a series of protein-creatinine tests It should be possible in this way to accumulate uniform material for an interpretation of proteinuria better founded than the first attempt here offered

TABLE 76 —INFLUENCE OF VARYING LEVELS OF PROTEIN INTAKE UPON THE PROTEIN CREATININE TEST

Experimental condition	Date	Rate of glomerular filtration cc per min	Protein elimination mg per hr	Protein in glomerular fil rate mg per 100 cc
Grace C-n				
Diet				
High protein	5–21	88	709	14 6
High protein	6 10	48	793	28 5
Low protein	6 12	19	588	52 1
Low protein	6 13	23	586	41 9
High protein	6–18	24	738	51 7
Mrs B-y				
Diet				
Ordinary	4 9	139	123	1 55
Moderately high protein	5–28	108	311	4 77
High protein	6–18	111	405	6 07
Low protein	6–22	91	207	3 68

The variations in filtration-rate deserve independent discussion The decline in rate in Grace C-n (Table 76) does not indicate that

the patient was rapidly progressing toward uremia Her subjective condition was most satisfactory She traveled and played nine holes of golf, and there was no symptomatic correlation with the filtration-rate *The patient was not hospitalized during the experiments,* only spending the forenoons on a bed in the laboratory It is amazing to find a drop from 48 to 19 cc minute filtration in two days following the change from high to low protein diet * In this connection one recalls the clinical experience that chronic nephritics frequently do poorly when hospitalized on low protein diet but improve when they return home to more liberal dietary habits The authors do not interpret the rapid changes in Grace C-n as indicating a corresponding anatomical deterioration, but see in [illegible] exaggerated in

[illegible]

larly the increase from 29 to 52 mg per 100 cc on change from high to low protein diet and marked decrease in protein output Can this changed permeability for protein also be interpreted on the basis of alteration in function without change in structure?

One interpretation which suggests itself from the correlation of the row of figures for protein output with either one of the rows for minute filtration or protein concentration in the filtrate is that the proteinuria is entirely hematogenous, *like the creatinuria a* certain amount of the blood proteins being so altered that they escape through the kidney, in high or low concentration, according to the functional capacity of the kidney—an idea in accord with Epstein The authors hesitate unreservedly to accept this interpretation, though their discussion in the next and last section leads in this general direction In addition at least two renal factors might be considered as *partially influencing these phe-*nomena, the rate of blood flow through the capillaries and the blood-pressure in the capillary loops of the tuft That this pressure

[illegible]

tion may be carried on

[illegible]

* Rehberg has correlated changes in filtration rate with changes in concentration of the total plasma proteins In Grace C-n the protein changes are sufficiently complicated to discourage the pursuit

[illegible]

Thus we find that in the protein-creatinine test the level of the protein intake may greatly influence the result, and evidently in an irregular and possibly unpredictable way depending on the [illegible]

inadvisable even as a temporary measure and others where it will appear impossible to the patient to take such a diet

The percentage distribution of albumin and globulin in the protein-creatinine test should be referred to briefly Table 75 shows in a general way a high globulin content in all cases with reduced filtration-rate and high protein concentration in the glomerular filtrate, while the globulin content may be high or low in instances of high filtration-rate and low protein concentration in the glomerular fluid This is in harmony with the discussion in the preceding section

Summary and Discussion —In the experiments reported on the preceding pages it has been easy to demonstrate the rôle of hematogenous factors in proteinuria and difficult to be sure of renal factors We have seen [illegible]
diet and promptly come [illegible]
all appearance as a pur[illegible]
irritation or damage

This response to altered protein intake did not occur in an untreated patient with myxedema and heavy proteinuria, but on administration of desiccated thyroid during high diet the patient showed increased proteinuria for nine to ten days, *in lieu* of increased nitrogen elimination, ordinarily observed and interpreted as due to mobilization of stored protein

Proteinuria was found temporarily to increase on change from resting recumbent position to active walking about, and to decrease upon the administration of sodium citrate, while sodium chloride and calcium chloride were without effect Injection of arsphena-

mine likewise had no effect Fever increased the loss of *protein* as did blood transfusion

High diuresis and transition to low diuresis had no effect upon *protein elimination* but sudden transition from low to high diuresis was apt to bring about a slight and transitory increase Feeding large amounts of urea might or might not cause a moderate increase in protein elimination

The facts are in harmony with the assumption of the *glomeruli* as the foci of protein leakage The behavior of the protein elimination during dilution-concentration tests particularly corroborates the assumption *Combination of the rate of protein elimination with* the rate of glomerular filtration as determined by Rehberg's creatinine test permits calculation of the protein concentration in the glomerular filtrate and offers a measure of the degree of glomerular leakage Intracapsular protein concentrations thus arrived at exhibit marked negative correlations with the rate of glomerular filtration The rate of glomerular filtration influences the values for the intracapsular protein concentrations more than does the level of *protein intake*

Further discussion of proteinuria necessitates consideration of the plasma proteins Comparison of normal and abnormal plasmas reveals certain facts in regard to the biological behavior of the separate protein fractions *Arranged according to decreasing solu* bility (albumin pseudoglobulin II pseudoglobulin I euglobulin and fibrinogen) they are at the same time arranged essentially according to their order of magnitude in normal plasma (albumin, 100 pseudoglobulin I 23 pseudoglobulin II 17 euglobulin 17 and fibrinogen 7) and inversely according to variability of concentration (coefficient of variation under abnormal conditions albumin 37 pseudoglobulin I 38 pseudoglobulin II 38 5 fibrinogen 107 and euglobulin 120)

As shown by other investigators they are as first arranged also arranged according to increasing molecular weights according to decreasing osmotic effect and as far as known according to decreasing base binding capacity

According to their behavior under pathological conditions the fractions may be combined into three groups albumin the pseudoglobulins and the euglobulin fibrinogen

There is no reason to assume that low albumin conte[illegible] failure of normal synthesis all evidence pointing *to an extraneous cause in the form of leaking kidneys* In myeloma only (page 534 V G) has pathological suppression of plasma albumin been observed

unassociated with loss of albumin through the urine In albumin depletion rapid albumin synthesis following high protein feeding may occur, but it is not clear why this is only rarely observed a rather slow increase being the rule An almost complete albumin depletion is compatible with life but as far as known always accompanied by large and unmanageable edema Even in this situation sufficient water is retained in the vascular system to protect against any marked polycythemia a situation assured by the hydration

min extraneously decreased the pseudoglobulins constitute the most constant factor of the plasma They participate neither in the reactions of the albumin nor of the euglobulin fibrinogen

The euglobulin fibrinogen consisting of the largest molecular aggregates of the plasma show by far the greatest instability For fibrinogen the known function of which consists in its easy conversion into fibrin this might be essential The euglobulin and fibrinogen vary together or independently of each other but hardly reciprocally we have sometimes found one or the other decreased mostly both are increased and the range over which they

Experiments have demonstrated the correlation of decreased stability of the blood suspension with increased globulin fibrinogen content The relationship between euglobulin fibrinogen content and the level of protein intake though possibly equally marked under a variety of conditions has been demonstrated in renal disease only In this condition the euglobulin fibrinogen content is markedly increased independently of the protein intake but especially high values are observed where the protein intake has been maintained high and spectacular diminutions follow within two to four days upon the discontinuation of the high diet

Thus at least three entities with different biological behavior are distinguishable in the plasma proteins The last discussed group made up of large aggregates possesses the least stability As to the mode of the building up of these groups the observations allow little insight into the synthetic machinery A few observations at Woods Hole and scattered reminiscences from the literature

have given the impression that globulin is phylogenetically the oldest blood protein Is it also the mother substance for the smaller and more stable plasma proteins or is each the result of separate synthesis?* Certain behavior of the urinary proteins suggests the latter alternative

It has long been known that the qualitative and quantitative composition of the urinary proteins does not reflect the proportions of the proteins in the plasma It might be assumed that the gross difference in composition is due to certain physical rather than chemical properties of the protein fractions manifesting themselves in contact with a glomerular membrane no longer completely impermeable to colloids of the order of magnitude of the normal plasma proteins As to these properties of the proteins and as to the changes in the glomeruli nothing direct can be said Unlike the situation in Bence-Jones proteinuria (see page 543) we deal in ordinary proteinuria with a graded permeability difficult to define further The authors have suggested that the proteinuria resulting from this abnormal permeability might be influenced by the rate of glomerular blood flow and by variations in glomerular blood pressure The calculations based upon the protein-creatinine test suggest a wide range in the degree of leakage and particularly indicate a sur well preserved kidneys In ular leakage is the greatest to the proportions of the plasma proteins though even here *the difference is* This

a difference from the situation in which kidney function is preserved Here the urinary proteins do not always differ from what is observed *in renal insufficiency* but the pattern is not fixed and might be varied within wide limits not *according to the apparent composition* of the plasma but according to the intensity with which the plasma proteins are being built up under the influence of a high level of protein assimilation

Two types of variations have been observed In the first type most frequently observed in the authors material the urinary protein during ordinary or low protein *diet* may consist almost entirely of so on high diet the albumin in e other plasma fractions inclu ady present *increase* more than the albumin producing a *pattern approaching* that in renal insufficiency Shift to low diet *will restore the original* pattern This type may be found in mild conditions where the body proteins are not severely depleted and also in conditions with

* See Howe in Phys ol Rev vol 5

increase—the reason for the authors caution not to interpret the response to fever necessarily as altogether renal

In the second type the urinary proteins show the reverse response to high diet, the albumin increases more than the other fractions This has been observed in severe protein depletion and marked positive nitrogen balance It was seen also in one instance, tenta-

It remains to discuss the significance of the solubility of the urinary albumin as compared with the albumin in normal and pathological plasma In the urine from a severe nephritic with high glomerular permeability as defined above the slope of the salting-out curve between 1 55 and 1 7 M Na_2SO_4 may differ very little from the slope in normal or nephritic plasma The curve of pathological plasma frequently is steeper than that of normal plasma The salting-out curve from urine in cases of nephrosis or chronic nephritis with fairly normal function and low glomerular permeability for protein differs from the preceding ones by its horizontal course This means that under the latter circumstances the urinary albumin has a higher solubility than the plasma albumin indicating that it consists of smaller molecules It is characteristic of the urinary protein in some cases of nephrosis and nephritis to contain two fractions chiefly of widely different solubility, a small amount precipitating as pseudoglobulin I and the remainder still fully soluble in 1 7 M concentration of Na_2SO_4 the highest concentration obtainable with this salt Where with $(NH_4)_2SO_4$ this albumin starts to come down has not been investigated, for lack of a method that the authors dared to trust for this purpose

This characteristic of urinary albumin gives the clew to the correlation of proteinuria with protein intake instead of with plasma proteins The following interpretation is offered The albumin fraction of the plasma includes molecules of different solubility and size Whether this holds also for the other fractions is not clear On high protein intake particularly in positive nitrogen balance, these smaller molecules are markedly increased Whether this means that under conditions of rapid protein synthesis they are discharged into the circulation before they have been built up to full

size the authors do not know It is not plausible that after they have entered the circulation they become coupled together to form larger aggregates neither is it plausible that they are just passing through the blood stream to be used as building stones in other tissues On discontinuation of high protein intake their amount rapidly and markedly decreases in the plasma On slight damage to the glomerular capillaries these small molecules will be the first ones to pass through the filtering membrane This constitutes a *selective* drain on the plasma albumin which deprived of its most soluble molecules shows a steeper slope between 1 55 and 1 7 M Na_2SO_4 than normal plasma Under the influence of this drain the plasma protein synthesis becomes accelerated small molecules are released and rapidly removed through the kidney a vicious circle is set up and in spite of high protein intake the albumin regeneration remains retarded With experimental and clinical evidence supporting this course of events the authors have not been convinced about the necessity to assume with Epstein the operation of an erroneous protein synthesis for the pathogenetic explanation of nephrosis Whether mild glomerular injury with low capillary permeability for protein causing a prolonged and selective drain on the plasma albumin alone offers an adequate explanation of the complicated clinical picture called nephrosis—on this point the authors experiments give no answer

APPENDIX

It might be a procedure open to criticism to report experiments as comprehensive as those above without appending a brief clinical account of the patients studied

CASE 1 —Mr B I aged forty four years Italian workman entered the Peter Bent Brigham Hospital (Med No 25754) for the third time April 23 192[illegible]

Nocturia in 1923 severe left side pneumonia January 1924 Transient swelling of ankles March 1924 2000 cc fluid removed from left chest about the same time the same amount removed in June 1924 persistent edema of legs ever since also pain in left side of chest more or less con t[illegible] Admitted to the Peter Bent Brigham Hospital August 20

[illegible]

phthalein tests varied from [illegible] to [illegible] per c[illegible]
1924
Took calcium chloride at home edema almost disappeared weight [illegible]

[illegible]

reported Condition otherwise as before Discharged February 26 1925 Remained in bed at home save for occasional short walks Weight increased from 148 to 172 pounds

Readmitted April 23 1925 Discharged November 20 1925 Height 162 cm Tonsils not enlarged or diseased Symmetrical expansion of

or below 130 90

This history calls for little comment In describing the experiments on page 478 the patient was presented as an instance of nephrosis The clinical picture at the time of the experiments is well characterized by this name Here we are not concerned about the ultimate outcome of the disease or the finer histological appearance of the glomeruli But attention shall be called to two facts one clinical and one of laboratory nature (1) There was before the reported experiments but after the patient had been sick for more than a year already a short period when the blood pressure was elevated and this period was terminated by pseudouremic convulsions and their sequelæ (2) There was considerable variability in the results of the phenolsulphonephthalein test On increased protein intake the test jumped from 25 to 40 per cent The authors wish to correlate this with the behavior of the Rehberg test in Grace C n (Table 76 page 513)

weeks in bed only to reappear more marked after acute rhinitis with slight

some granular casts but no rec

The non-
t gave the
lmination
ed protein

The clinical picture and functional performance at the time of

At the

CASE 3 —Edwin T r aged twenty five years, an English born grocery clerk, entered the Peter Bent Brigham Hospital (Med No 26074), on

because of albuminuria Entirely unaware of any trouble when re ... for the insurance January 18 1925 severe attack of grippe with sore throat and hoarseness Nine days later face began to swell the swelling gradually extending all over the body In the county hospital swelling

Edema increased, it apparent cause disappeared com 1926 was getting anything, feeling

The remark as to diagnosis under the preceding history seems applicable even to this patient

CASE 4 — Mr B., aged fifty two years a German-born salesman,

occasional hyaline and granular casts and white cells no red cells ever demonstrated with certainty

The patient died May 27 1927 in a sanatorium His last months of life were characterized by persistent vomiting the cause of which is not

An instance which may well be called nephrosis in chronic tuberculosis and where amyloidosis is generally assumed to exist but not always found

condition that might be a precursor of an acute or a chronic nephritis He reports no edema of eyelids or ankles no nocturia no polyuria and never observed blood in the urine

cent

Discharged November 18 1934 At that time only a trace of albumin was present in the urine and the phenolsulphonephthalein test was 60 per cent for two hours

Patient returned for examination at frequent intervals and at these *times his urine usually showed albumin casts and white blood cells*

He was in the hospital for further observation from January 22 to 30 ... few casts no ... normal He ... ut no edema ... weather so did not work after the onset of winter

Readmitted for observation July 7 and discharged July 12 1930

Physical ...
Murphy ...
2+ to 3+
Blood ure...
hours Ophthalmoscopic examination Disk round ...

vessels

Patient reported occasional puffiness of face and eyelids otherwise no symptoms of nephritis

This case should not be confused with syphilitic nephrosis as that picture frequently has been described Neither is there any reason to correlate the urinary finding with the antisyphilitic As treatment nor with the small amount of Hg treatment that the patient might have received In the absence of other symptoms of mercurialism one should have expected the albuminuria if due to mercury rapidly to disappear on the discontinuation of treatment This *otherwise symptom free albuminuria in syphilis* of which we observed a second instance at the Boston dispensary is an obscure condition though it has long been known *

Case 7 —Mrs A-e aged fifty fi e years Norwegian born housewife entered the I ... H ... 52 0 April 1 1926 s spected of

th scales fine like
Slight edema of
Heart on 6-foot

* Laurent C Presse med p 716 May 19 5

After four years February 13 1930 the patient was gone over in detail She had been taking 2 grains desiccated thyroid twice daily regularly The basal metabolic rate was +4 Blood pressure 140/76 Hemoglobin 90 red cells 4 860 000 Ophthalmoscopic examination suggested only a beginning arteriosclerosis of the retinal vessels Urine contained no albumin The plasma protein which was depleted in 1926 (see Fig 106) now was 8 per cent with
3 87 gm total globulin
following composition
pseudoglobulin II or 1
cent and fibrinogen 1
this fraction thus still differing from normal values

In 3 of the first 4 cases of this series the basal metabolic rate was studied and found below normal In this patient the clinical picture is entirely different from that of the preceding cases of nephrosis Here is a picture of asthenia chiefly, which in combina

of the present authors (Scriver) observed no influence of thyroid medication upon the albuminuria of true nephrosis, at variance with what has been described by Epstein *

to suppuration relieved by ... weeks

* Lewis D S and Scriver W de M Ann Int Med 2 66–8 19 8

The patient presented generalized marked edema the breathing was difficult he was able to move with aid only Mentally he was somewhat cloudy Weight 92 4 kg There was a 5 cm large carbuncle on the back of the neck which was incised and drained The size of the heart was

his no e May 24 w ere he died May 25 Diagnosis Acute or subacute nephritis

Instead of discussing the diagnosis which seems superfluous the authors want to remind the reader of what Addis calls renal failure casts * Epithelial casts were repeatedly observed in the urine from this patient but the broad dark casts in which interest has been revived through Addis studies were not described perhaps because they *did not look for them* While earlier clinicians mentioned them in contracted kidneys chiefly Addis has observed them also in subacute forms

That isosthenuria specific gravity around 1 011 does not occur in renal failure of acute nephritis has been brought out by Volhard and is illustrated in this patient with specific gravity of 1 017 to 1 021 But the concentration accomplished by the kidney is estimated too high if based on the specific gravity since the protein content of the urine was high between 1 8 and 2 9 per cent which corresponds to a specific gravity of the protein solution alone of 1 005 to 1 008 This taken into account the kidneys produced a urine but little better than isosthenuria

* Addis T J Am Med Assn 84 1013–1015 19 5

REFERENCES

3a ACHARD C AND CAILLARD I 1901 Expériances sur la perméabilité du rein sain ou malade à la caséine Compt rend Soc de biol 53 123 124

3b BATTY S H 1920 An unusual form of turbid urine due to the presence of lecithin globulin Proc Roy Soc Med 13 Pt II Sect of Med 105–107

4 BENCE-JONES H 1847 Trans Roy Soc London

5 BERGLUND H AND SCRIVER, W DE M Unpublished data

6 ——— 192 Studies in albuminuria Proc Am Physiol Soc Am J Physiol 76, 190

7 BIETER, R N 1931 Albumin uria in glomerular and aglomerular fish J Pharm and Exp Therap 43 407–412
8
sies 3
9
Effect
10
11
Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy London Longman Rees Orme, Brown and Green Pt 4 vol 2 (18
th
be
occ
m
curves for urinary edema fluid and blood plas a proteins
857–867
14 COHN E J 1925 The physical chemistry of the proteins Physiol Rev 5 349–437
16 COTUNNIUS D 1770 De ischiade nervosa commentarius Vienna Q ot fr Darwin
17 CSATÁRY A 1890 Ueber Globulinurie Deutsch Arch f klin Med 47 159–18?
18 ——— 1891 Ueber Globulinurie Deutsch Arch f klin Med 48 358–368
19 CULLEN G E AND VAN SLYKE D D 1921 Determination of the fibrin globulin and albumin nitrogen of blood plasma J Biol Chem 41 587 597
20 CUSHNY A R 1926 The Secretion of the Urine 2d ed London Longmans Green & Co
21 DARWIN E 1800 Zoonomia or the Laws of Organic Life 2 vols Dublin, P Byrne 2d Amer ed by Thomas & Andrews Boston 1803
22 DOCK W 192? Some early observations of albuminuria Ann Med Hist 4 287
23 DRESSLER 1854 Ein Fall von intermittirender Albuminurie und Chromaturie Virchows Arch f path Anat 6 264 266
24 DUNN H L 1929 Application of statistical methods in physiology Physiol Rev 9 275–398
25 EPSTEIN A A 1912 A contribution to the study of the chemistry of blood serum J Exp Med 16 719–731
26 ——— 1913 Further studies on the chemistry of blood serum J Exp Med 17 444–45?
27 ——— 1928 Ueber Diabetes albuminuricus die sogenannte chro
nosk 44 31–55
925 Blood serum globulin in leprosy
1923 A functional and anatomical
the kidney J Exp Med 37 83
3 GOODPASTURE E W brinogen II The association of liver and intestine in rapid regeneration of fibrinogen Am J Physiol 33 0–85

36 HAMMARSTEN O 1878 Leber das Paraglobulin Arch f d ges Physiol 17 413

Alla 65 2 1 230

40 ———— 1882 Globulinbestimmungen in Ascitesflussigkeiten Arch f exp Path u Pharmakol 16 133 142

41 HOFMEISTER, FR 1888 Zur Lehre von der Wirkung der Salze II and III Arch f exp Path u Pharmakol 24 247 25 1

42 HOWE P E 1925 The function of the plasma proteins Physiol Rev 5 439–476

43 HUPPERT 1896 Leber einen Fall von Albumosuria Ztschr f physiol Chem 22 500–507

44 ———— 1898 Ueber den Noel Paton schen Eiweisskorper Centralbl f d med Wissensch 36 481–483

45 HURWITZ S H AND MEYER K F 1916 Studies on the blood proteins I The serum globulins in bacterial infections and immunity J Exp Med 24 515–546

46 *HURWITZ S H AND WHIPPLE G H 1917 Studies on the blood* proteins II The albumin-globulin ratio in experimental intoxications and infections J Exp Med 25 231 253

46a HYND A 1925 Nature of urinary protein with special reference to

ms

nk
ren

ra
tein

nce
J

104 41-61

54 LEHMANN J C 1864 Leber die durch Einspritzungen von Hühnereiweiss in Blut hervorgebrachte Albuminurie Virchows Arch f path Anat 30 593–598

55 LEHMANN J C 1866 Studien uber Essigsaurealbuminat Virchows Arch f path Anat 36 110
56 ———— 1866 Zur Chemie des Eiweissharns Virchows Arch f path Anat 36 125 131
57 LEWITH S 1887 Zur Lehre von der Wirkung der Salze I Arch f exp Path u Pharmakol 24 1 16
58 LINDER G C LUNDSGAARD C AND VAN SLYKE, D D 1924 The concentration of the plasma proteins in nephritis J Exp Med 39 887 920
59 MAGNUS LEVY A 1904 Ueber Myxodem Ztschr f klin Med 52 201–256
60 MEILLÈRE G AND LOEPER M 1901 Variations du rapport des

... Dis 22 1 27
63 OSMAN, A A 1926 Preliminary observations on the treatment of nephritis with œdema by means of large doses of alkalies Guys Hosp Rep 76 412–425
64 POHL J 1886 Ein neues Verfahren zur Bestimmung des Globulins im Harn und in serosen Flussigkeiten Arch f exp Path u Pharmakol 20 426–438

Scand Suppl II 1 704
68a SELLARDS A W AND MINOT G R 1916 Injection of hemoglobin in man and its relation to blood destruction J Med Res 29 469–494
68b ———— 1917 Preparation of hemoglobin for clinical investigations J Med Res 32 161–170
69 SENATOR H 1874 Ueber die im Harn vorkommenden Eiweisskörper und die Bedingungen ihres Auftretens bei den verschiedenen Nierenkrankheiten, uber Harncylinder und Fibrinausschwitzung Virchows Arch f path Anat 60 476–505
70 ———— 1881 Albuminurie 2d ed 1890 Berlin English translation as vol 110 of the New Sydenham Soc Monographs 1884
71 ———— 1895 Die Erkrankungen der Nieren Nothnagels Spec Path u Therap 19 1
72 SIA R H P AND WU H 1921 Serum globulin in kala-azar China Med J vol 35 No 6
73 SØRENSEN S P L 1925 Proteins Lectures given in the United States of America in 1924 The Fleischmann Laboratories 1925
74 STARLINGER, W AND WINANDS E 1928 Ueber das Verteilungsverhaltnis der zirkulierenden Eiweisskorper im Verlaufe krankhafter Zustande Ztschr f exp Med 60 138 208
75a THOMPSON W O 1926 Blood volume in myxedema J Clin Invest 2 477 520
75b WALLIS R L M 1920 Non nephritic albuminuria Proc Roy Soc Med Pt II Sect of Med 13 96–104
... 1914 Fibrinogen I An investigation concerning its ... 33 50–69
... Fibrinogen of the blood ... poisoning J Exp Med 13
150–161
78 WIDDOWSON E M 1933 A comparative investigation of urine and serum proteins in nephritis, Biochem J 27 1321 1331

CHAPTER XXXI

BENCE-JONES PROTEINURIA *

By GRACE MEDES PH D

WITH

THE PARTIAL COLLABORATION OF

HILDING BERGLUND M D

AND

THE TECHNICAL ASSISTANCE OF

MARY R NEEMES B S

CHEMICAL CHARACTERISTICS OF BENCE-JONES PROTEIN

Conditions Affecting Tests for Bence Jones Proteins The usual test for the demonstration of Bence-Jones protein in urine is a modification of the heat and acetic acid test as described by Magath (page 441) The urine is slightly acidified with acetic acid and

temperatures is incomplete rendering the identification of the protein less simple The difficulty is often ascribed to the admixture of

the conditions of the experiment These conditions are elucidated by the behavior of Bence-Jones protein in salt free solution

Applying their studies to salt free solutions of the protein [illegible]

* Aided by a grant from the Research Fund of the Graduate Medical School of the University of Minnesota

that in strongly alkaline solutions no precipitation is discernible They apparently did not observe that at low degrees of alkalinity the protein behaves very much as in slightly acid solution the coagulation appearing at a somewhat higher temperature with a tendency to redissolve as the boiling point is approached

Magnus Levy[26] was the first to recognize that the characteristic behavior of Bence-Jones protein depends upon the simultaneous presence of other urinary constituents He considered urea as the compound of chief importance Hopkins and Savory confirmed the role

demons

in low c

solubility of the protein at high temperatures Monovalent salts like NaCl have a slight effect The dissolving power increases in neutral (very faintly acid) solution with increase of valency of either the acid or the basic constituent For complete clearing at the boiling point at least dibasic ions are essential In higher concentrations the same salts are effective salting out agents When magnesium sulphate is present at approximately one-half saturation the heat coagulum induced at 50° C no longer completely dissolves at 100° C When about two thirds saturation is reached the coagulum does not dissolve at all Ammonium sulphate has similar action

Equal to the salt content in importance is the hydrogen ion concentration Hopkins and Savory worked at three different pH one neutral or slightly acid a second more acid obtained by adding 1 drop of glacial acetic acid to 200 cc of the neutral fluid and the third an alkaline solution consisting of the original dialyzed material They state that it was faintly alkaline to litmus Malengreau[28] who more extensively studied the influence of different pH upon the salt effect states that the acidity of Hopkins and Savory s acid solution was scarcely sufficient to bring it outside of the isoelectric zone Hopkins and Savory found the dissolving action in acid solution to be favored by the increasing valency of the positive ion and in alkaline solution by the valency of the negative ion Malengreau s observations led him to the opposite conclusion All are agreed that some association exists between salt and protein and that the physical properties are markedly different at high and at low temperatures because of differences in this association or in the ionization of the resulting compound Various values for the isoelectric point have been reported Hewitt[15 16] at between pH 5 5 and 6 Willheim[47] at pH 4 05 to 4 75 and Svedberg[38 39] at pH 5 18 to 5 ?

Considering the variability of urines with respect to hydrogen ion concentration and salt content all specimens cannot be expected to show a complete reversibility of the solubility without adjust

ment of one or both factors Possibly the most successful attempt at such an adjustment has been described by Osgood and Haskins [29] To 5 cc of urine in a test-tube they add 1 cc of 50 per cent acetic acid and 3 cc saturated (about 30 per cent) sodium chloride A precipitate appearing at room temperature on addition of both these reagents strongly suggests Bence-Jones protein They state that a precipitate may also occur in urines containing globulin in amounts of 0 38 gm per liter, but point out that such urines are uncommon They submit the precipitate obtained, as described above, to the usual heating and cooling

In the authors' laboratory this heating and cooling, when done in the presence of urine, has been found so unsatisfactory that the authors immediately proceeded to the further test suggested by

tested for urinary albumin and globulin For this purpose 1 cc of 50 per cent trichloracetic acid in the cold is employed In all the cases except 1, to be described below this portion of the test has proved negative

Solubility of Plasma and Urinary Proteins in Bence-Jones Proteinuria —The authors have studied the solubility of plasma and urinary proteins in 8 patients with Bence-Jones proteinuria. (Table 77) Seven patients had multiple myeloma, 1 of them (5, A G) presented an apparently solitary destructive process of less than a hen's egg size in the left humerus which had caused a pathological fracture All other bones, particularly vertebræ and skull, were roentgenologically normal The other patient (6, M G) had a diffuse amyloidosis Extensive roentgen-ray studies of his skeleton failed to reveal any evidence of myeloma Unfortunately no autopsy was obtained, but up to the time of death the clinical picture was clearly that of amyloidosis The qualitative test for Bence-Jones protein as described above, was tried on the plasmas of all but No 4 and found negative The test was positive on all urines, and after adjustment of acidity and salt content it showed in every case complete disappearance of the precipitate at the boiling-point

It has seemed desirable to devise a mode of study by which statements, based on the qualitative test only, could be complemented

* If the Bence-Jones protein is very concentrated the urine must be diluted before this test is applied In some of the material a dilution of 1 part urine to 4 parts of water was employed

by quantitative procedures, allowing a comparison of cases observed by different investigators The ideal procedure would be the

TABLE 77

Subject	Na_2SO_4 molar conc	Plasma proteins gm per 100 cc	Urinary proteins			Conventional plasma nomenclature
			Mg per 100 cc	Mg per 24 hrs	Unprecipitated protein per cent	
1 G G (37406)	0.75	0.13	0	0	100.00	Fibrinogen
7/29/26	1.00	1.48	12.0	95	99.11	Globulin: Euglobulin
N P N 36 mg	1.25	1.41	494.0	4 450	54.87	Globulin: Pseudogl I
	1.55	1.49	564.0	5 075	4.36	Globulin: Pseudogl II
		2.81	*49.0*	438		Albumin
		7.32	1118.0	10 058		Total protein
2 A B (38759)	0.75	0.21	0	0	100.00	Fibrinogen
2/14/27	1.00	0.79	2.9	44	99.69	Globulin: Euglobulin
N P N 44 mg	1.25	1.67	708.1	10 869	5.62	Globulin: Pseudogl I
	1.55	0.88	42.3	650	0	Globulin: Pseudogl II
		4.41	0	0		Albumin
		7.96	753.3	11 563		Total protein
3 H H	0.75	5.22	0	0	99.90	Fibrinogen
8/29/28	1.00	7.41	0	0	99.90	Globulin: Euglobulin
N P N 40 mg	1.25	0.59	5.8	50	43.10	Globulin: Pseudogl I
	1.55	0.38	2.9	25	14.70	Globulin: Pseudogl II
		2.50	*1.5*	*13*		Albumin
		16.10	10.2	88		Total protein
4 M L (58011)	0.75	1.52	2.0		99.28	Fibrinogen
3/6/31	1.00	0.55	23.0		81.04	Globulin: Euglobulin
N P N 109 mg	1.25	1.02	148.0		37.99	Globulin: Pseudogl I
	1.55	0.44	83.0		8.24	Globulin: Pseudogl II
		4.69	23.0			Albumin
		8.22	279.0			Total protein
5 A G (16183)	0.75	0.38	0		100.00	Fibrinogen
7/1/31	1.00	0.09	0		100.00	Globulin: Euglobulin
N P N 50 mg and 59 mg	1.25	0.72	668.0		22.40	Globulin: Pseudogl I
	1.55	0.90	193.0		0	Globulin: Pseudogl II
Rehberg 27 cc		*2.23*	*0*	*60 min*		*Albumin*
		4.32	861.0	766		Total protein
6 M G (61183)	0.75	0.78	0	0	100.00	Fibrinogen
11/2/31	1.00	0.38	2.0	21	99.60	*Globulin*: Euglobulin
Serum Ca 12.7 mg	1.25	0.89	118.0	1 233	*75.20*	*Globulin*: *Pseudogl I*
N P N 40 mg	1.55	1.55	363.0	3 793	0	*Globulin*: Pseudogl II
Rehberg 115 cc	1.70	0.28			0	Albumin
		3.75				
		7.63	483.0	5 047		Total protein
7 C K (61326)	0.75		25.0		90.00	Fibrinogen
(a) 11/10/31	1.00		11.0		84.10	Globulin: Euglobulin
Serum Ca 13 mg	1.25		2.0		83.30	Globulin: Pseudogl I
Rehberg 104 cc	*1.55*		*26.0*		71.80	Globulin: Pseudogl II
	1.70		39.0		54.60	Albumin
			124.0	60 min		
			227.0	579		Total protein
(b) 11/17/31	*0.75*	*0.54*	*0*	*0*	*100.00*	Fibrinogen
N P N 34 mg	1.00	0.47	26.0	538	97.00	Globulin: Euglobulin
	1.25	1.59	42.0	869	92.10	Globulin: Pseudogl I
	1.55	0.66	139.0	2 877	76.00	Globulin: Pseudogl II
	1.70	0.28	321.0	6 645	38.80	
		3.47	*335.0*	*6 935*		*Albumin*
		7.01	863.0	17 864		Total protein
8 C H	0.75	8.42	0		100.00	Fibrinogen
4/6/33	1.00	4.58	0		100.00	*Globulin*: Euglobulin
N P N 47 mg	1.25	2.50	306.0		*46.10*	*Globulin*: Pseudogl I
Serum Ca 13.6 mg	1.55	0.51	236.0		4.60	*Globulin*: Pseudogl II
Rehberg 80 cc	1.70	0.41	26.0			
		1.16				Albumin
		17.58	568.0			Total protein

determination of the solubility curve of the purified protein as determined for serum albumin in the works of Chick and Martin and of Sørensen With this requirement very few cases would be studied It was hoped that, without purification of the urinary protein the salting out with different concentrations of Na_2SO_4 would give characteristic solubility curves to be compared with solubility curves of plasma proteins and of urinary proteins in other types of proteinuria The results as represented in Figs 111 and

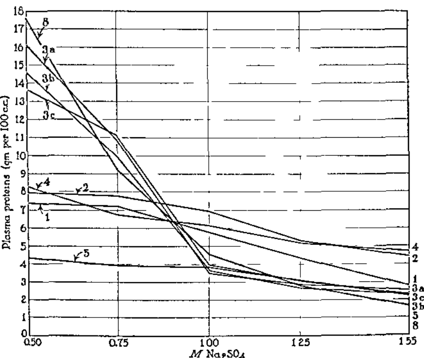


Fig 111 —Solubility of plasma proteins in multiple myeloma (The figures refer to patients in Table 77)

112 are more clear cut than anticipated Fig 111 showing the concentration of the plasma proteins for each point of the abscissa gives the amount of protein remaining in solution at the given concentration of Na_2SO_4 Fig 112 gives a corresponding expression of the solubility of the urinary protein but the wide variations (from 10 to 1118 mg per 100 cc) in the amount of protein rendered a graphic presentation of the absolute values impracticable, the figure instead presents the percentage of urinary protein remaining unprecipitated at each Na_2SO_4 concentration In all of the samples

except 7 (C. K.) the Bence-Jones protein is practically completely precipitated between 1 and 1.55 molar concentration of Na_2SO_4. 50 per cent or more is precipitated between 1 and 1.25 molar in Case 3, in Case 5 78 per cent and in Case 2 95 per cent came down within this narrow range of *concentration*. Chapter XXX on Proteinuria contrasts the solubility of Bence-Jones protein against anything observed in other proteinurias. In regard to the sharp angles present in Fig. 112 for Case 4 at 1 molar concentration and for Cases 2 and 5 at 1.25 molar concentration the precipitations

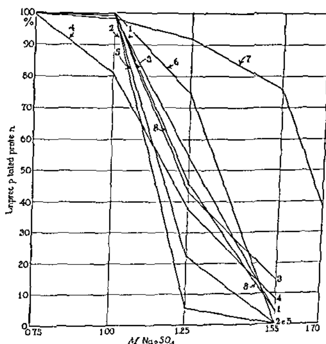


Fig. 112. Solubility of Bence-Jones proteins in the urine in multiple myeloma. (The figures refer to patients in Table 77.)

were not carried out with sufficiently small intervals between the salt concentrations to warrant any conclusions about these bends of the curves. As may be seen from Table 77 and Fig. 112 the solubility of the protein in Sample 7 shows a marked *difference* from that of the others, 76 per cent remaining in solution at a molar concentration of Na_2SO_4 of 1.55 and 39 per cent being unprecipitated at a molar concentration of 1.7. This indicated that we were dealing here with a protein of widely different properties but definite proof was not obtained until later as described on page 538.

For purification of the protein they were salted out from urine

with Na_2SO_4 In all but Case 7, a concentration of 1 55 molar Na_2SO_4 produced almost quantitative precipitation In Case 7 the urine had to be saturated with $(NH_4)_2SO_4$ in order to salt out the protein completely The urine was allowed to stand about a week, until the protein had settled, when the urine was syphoned off, the precipitate dissolved in water and Na_2SO_4 or $(NH_4)_2SO_4$ added to the same concentration as was employed previously This alternate salting out and dissolving was repeated about eight times The further purification was carried out by a method suggested by

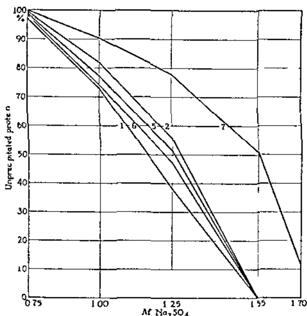


FIG 113 —Solubility of purified Bence-Jones proteins in solutions of sodium sulphate (The figures refer to patients in Table 77)

Dr R A Gortner The pH was adjusted to the isoelectric point of the protein the supernatant liquid was once again syphoned off and the protein transferred to cellophane tubing and dialyzed in repeated changes of water at about 5° C until the dialysate was sulphate-free (about one week) The cellophane sac was hung in a stream of warm dry air until the contents were reduced to a thick syrup The syrup was then poured into a Petri dish and dried to a powder in an oven at 40° C It was preserved in a refrigerator at 0° C and before using was dried to constant weight in a desiccator over H_2SO_4

Fig 113 represents the salting-out curves of 4 of these samples after purification As may be seen, Samples 1, 2, 5 and 6 present

to those delineated

maintains its peculiar

are dealing with a

protein of different constitution

In contrast to the urinary findings, the plasma proteins (Fig 111) show no precipitation beyond normal limits within the concentrations of 1 and 1 55 molar Na_2SO_4 The plasma curves when compared w th the

of any

in the l

an abnormal tissue and urinary protein rather than a blood protein (Abrikossoff and Wulff and others) A pathological synthesis of plasma proteins is demonstrated in Cases 3 and 6, in whom the protein concentrations were doubled, the excess amount being

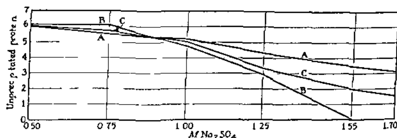


Fig 114 —Solubility of purified Bence-Jones protein in plasma *A* Normal plasma *B* purified Bence-Jones protein *C* mixture of plasma (*A*) with Bence-Jones protein (*B*)

precipitated between 0 5 and 1 molar concentration of Na SO_4 *viz* within the range of fibrinogen and euglobulin No attempts at isolation and identification of this large amount of extra protein were made except that it was clearly demonstrated that it did not behave like Bence-Jones protein In view of the unusual finding on the first case (3) the determinations were repeated twice with an interval of some days, all three determinations are reproduced

Fig 112, in spite of the difficulty in carrying out the determination upon such a small amount, shows a reasonably good agreement with the other curves The authors have found reference to one similar case (Perlzweig Delrue and Geschickter[32])

To be assured that Bence-Jones protein in blood plasma would not be precipitated in the euglobulin group the following experi

ments, depicted in Fig 114, were performed Curve *A* of the figure represents the solubility of plasma proteins in sodium sulphate as determined by adding 1 cc of normal plasma to ascending molar concentrations of the salt in 50-cc volumetric flasks *B* represents the solubility of a purified Bence-Jones protein so adjusted that 25 cc had approximately the same nitrogen content as 1 cc of plasma, 25 cc were used and made up to 50 cc in solutions of sodium sulphate to correspond with those in *A* In experiment *C*, 0 5 cc of plasma and 12 5 cc of the protein solution were employed It may be seen that within the limits of experimental errors, the added Bence-Jones protein precipitates out within the same regions in *C* as in *B*

It is surprising to find that in the 8 instances of Bence-Jones proteinuria in Table 77 the plasma proteins presented a most varied picture, there are represented in Fig 111 normal plasma protein massive increase of total protein due to increased fibrinogen

plasma, slight to heavy Bence-Jones proteinuria occurred without evidence of accumulation or presence of this body in the plasma The pseudoglobulins are the proteins least affected

Chemical Studies of Bence-Jones Protein —As to the chemical and biological entity of Bence-Jones protein the situation is perhaps best elucidated by Hopkins characterization of the protein as a uniform substance but not necessarily a chemical individual Hopkins and Savory analyzed side by side the material from 3 patients and found a satisfactory agreement in the amino-acids which could be determined with the greatest accuracy They therefore concluded that the materials were identical Luscher[22] working in Hopkins laboratory concurred in this opinion Wilson[44] worked on specimens from three sources one specimen which crystallized spontaneously while the others resisted all efforts toward crystallization On the basis of this difference and of immunological reactions studied by Bayne-Jones and Wilson Wilson holds that different Bence-Jones proteins exist The specimen studied by Wilson which crystallized spontaneously could also be recrystallized with ease Wilson reviews the cases in which attempts at crystallization have been successful and cites instances where investigators have interpreted crystalline deposits in *microscopic* sections from autopsy material as this protein Cohn[8] pointed out discrepancies in various analytical and anaphylactic results, and expressed uncertainty as to whether these discrepancies depend upon differences in the material studied or upon impurities of the preparations

A chemical study has been made in this laboratory of 6 samples

of Bence-Jones protein, from Cases 1, 2, 5, 6, 7 and 8 of Table 78 (Reported in part at the Biochemical Society, Cincinnati, April 1933) The proteins were purified as described above, and analyzed according to the nitrogen distribution method of Van Slyke [42, 43] Cystine values were checked by the colorimetric method of Folin and Ciocalteu [9] The results of these analyses are given in Table 78 together with Luscher's analysis of Bence-Jones protein and Drummond's figures for the proteins of normal tissues It may be seen that 5 of our series are similar (Cases 1, 2, 3, 5 and 8) and in close agreement with Luscher's The fifth (Case 7) is characterized by lower ammonia N, higher diamino-N, cystine, arginine and lysine being all increased, lower non-amino-N of the filtrate (proline and oxyproline), lower tryptophane, with tyrosine the same

TABLE 78 —COMPOSITION OF BENCE-JONES PROTEINS

(In Column A are given Lüscher's figures for a similar study The figures 1 2 5 6 7 and 8 refer to the number of the patient as given in Table 77 In Column B are Drummond's figures for normal tissues *)

	A	1	2	5	6	8	7	B
Amide N	9 43	9 25	9 30	9 40	9 35	9 45	5 20	5 82
Humin N	0 90	1 03	1 00	0 97	0 90	1 07	1 85	3 09
Total N of bases	23 11	22 83	23 05	22 87	22 58	22 90	30 06	30 71
Amino-N of bases	13 14	12 47	12 51	12 57	12 42	12 65	17 64	16 16
Cystine-N	1 25	1 41	1 43	1 45	1 47	1 45	2 04	0 93
Arginine-N	9 27	9 40	9 41	9 12	9 34	9 34	12 12	11 13
Histidine N	4 54	4 97	5 25	5 19	4 73	4 86	4 97	7 86
Ljsine-N	8 04	7 05	6 96	7 11	7 04	7 25	10 91	9 83
Total N of filt	66 84	66 74	66 74	66 72	66 78	66 61	63 21	60 82
Amino-N of filt	61 69	62 29	62 08	62 02	61 98	61 72	59 56	55 88
Tyrosine-N		3 36	3 36	3 39	3 35	3 35	3 40	
Tryptophane-N	2 44	1 90	2 12	2 03	1 97	1 07	1 01	
Non-amino-N of filt	5 15	4 45	4 66	4 70	4 80	4 89	3 65	4 94
Total N per cent protein		16 20	16 22	16 20	16 24	16 21	16 22	
Ash per cent protein		0 19	0 26	0 16	0 20	0 20	0 19	
Total N	100 28	99 85	100 12	100 37	99 61	100 03	100 3	100 40

* Drummond *Biochem J* *10 473 1916*

The molecular
in two different
half that of serum
the minimal weight as 12,250 or twice this 24 500, the latter figure being about one-half that of the minimal molecular weight they have given for serum albumin (45,000, and about one-third of the minimal molecular weight for serum globulin *(80 000)* Their calculation for Bence-Jones protein was made on the basis of Folin

and Looney's[11] tryptophane determinations and Hopkins and Savory's sulphur analysis It may be noted that they omitted in their calculations any consideration of the histidine content since this would lead to a molecular weight of 73 500, a figure that they considered too high Svedberg[39] using the ultracentrifuge, placed the molecular weight at 35 000 ± 1000, a figure approximately one half of his estimate for serum albumin (67,500) and one third that for serum globulin (103,800)

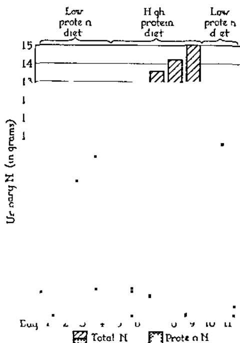


FIG 115 —Metabolism experiment Case 5 (C H on low high and low protein intake The output of Bence-Jones protein is approximately constant

The classification of Bence-Jones protein once a subject of lively discussion, calls for detailed consideration no more its character as a protein being agreed upon and its similarity and dissimilarity to the globulins having been repeatedly discussed The same might be said about the relation between protein intake and amount of Bence-Jones body lost in the urine Magnus-Levy, in prolonged metabolism experiments demonstrated a slight positive correlation between nitrogen intake and Bence-Jones excretion, and believes there is an exogenous as well as an endogenous factor

in Bence-Jones proteinuria The conclusion reached by Allard

cases extensively studied (Cases 1 and 8) the same seemed to be true Fig 115 *represents a metabolism experiment on the latter* On account of his extreme illness the experiment could not be prolonged

CLINICAL PATHOLOGICAL CONSIDERATIONS OF *BENCE-JONES PROTEINURIA* *

Special interest has been bestowed upon Bence-Jones proteinuria *because of the high incidence of chronic kidney disease in patients* suffering from multiple myeloma (Wallgren[44] Geschickter and Copeland[12]) Supporters (Th Fahr, Lichtwitz) of Epstein s theory of nephrosis as due to altered plasma protein by its leakage damag ing the kidney have seen in Bence-Jones proteinuria an analogy to the nephrosis Though the kidney lesions found in multiple myeloma might vary some instances have been classified as contracted nephrotic kidneys as conceived by Th Fahr (Thann *hauser and Krauss*[40]) *In this connection reference has also been* made to Longcope s work on the effects of foreign protein on the kidney in man Without denying the possible correctness fully or in part of this view of the relation between damaged kidneys and Bence-Jones proteinuria certain difficulties in its acceptance shall be discussed and another line pointed out for the investigation of the kidney involvement in multiple myeloma

The only convincing evidence of the presence of detectable amounts of Bence-Jones protein in *the circulating blood* was presented by Abderhalden[1] and by Wilson[48] Other investigators *i e* Jacobson[18] Perlzweig Delrue and Geschickter[32] Taylor Miller and Sweet[41] Magnus Levy[5] Hewitt[15,16] and Munzer[27] have re ported isolation of traces of a protein which possessed Bence-Jones *like properties* In view of the fact that many of these plasmas contain abnormally large amounts of euglobulin thereby imparting properties to the plasma quite different from those of normal plasma it is believed that isolation of a compound *with aberrant* solubilities

the about 7000 mg of total serum protein

tro
nes
ind

* With Hilding Berglund

In 3 of the authors cases unsuccessful attempts were made to demonstrate the protein in the blood

Turning to the situation in the urine it is important that Hopkins and Savory in their 3 cases and Folin and Denis in their case found no protein other than the Bence-Jones present in the urines they studied The authors have no evidence in their 8 cases of the presence of any proteins other than the Bence-Jones Thannhauser and Krauss[40] feel convinced that in their case a slight amount of serum proteins was present besides the Bence-Jones The only case among the authors records in which albumin was admixed with the Bence-Jones protein in the urine was one brought to their attention by Dr E T Bell who sent a sample of urine obtained postmortem It contained large amounts of protein which was about 80 per cent Bence-Jones protein and about 20 per cent albumin The

died of kidney

His serum prot

does not offer strong evidence of any etiological relation between

i shall further be

who during four

of Bence-Jones

protein daily When after this period of time autopsy was obtained

than serum albumin easily escapes through the glomeruli showing little or no accumulation in the blood In finding its way into the urine it leaves the glomeruli unharmed without causing any alteration in the permeability of the finer glomerular structure as evidenced by the frequent absence of detectable traces of serum albumin in the urine After at least 14 6 kilos of Bence-Jones protein had been filtered through the glomeruli (Hopkins and Savory Case A) the kidneys still appared normal and even in markedly contracted kidneys in myeloma the glomeruli on ordinary microscopic examination may show few scattered pathological changes only (Thannhauser and Krauss[40]) The Bence-Jones protein once having passed through the wall of the glomerular tuft should endanger the kidney no more no one as far as the authors are aware postulating any tubular reabsorption of protein

In rare instances abundant crystallization of protein has been

observed in the lumina of the tubules In 1 case of multiple myeloma (Lohlein[22]) Bence-Jones proteinuria was observed during life no other protein being present in the urine In 2 other cases Koch[19] and Rehsteiner[35] stated that no reason to assume Bence Jones proteinuria existed Ordinary albuminuria was present Glomerular changes as in glomerulonephritis were absent in all 3 cases The diagnoses of nephrosis were made It is important to note that the crystals were found in the tubular lumina only the interstitial tissue being free Binding evidence that they were formed during life and not immediately before or after death was present in all cases in the form of foreign body giant cells attacking the crystals in the lumina Kleine[20] has added another observation less clear cut than Lohlein s of crystalloid protein casts surrounded by giant cells in the renal tubules in a case of multiple myeloma with Bence-Jones proteinuria

The intratubular crystallization of protein is of interest in connection with Wilson s case of spontaneous crystallization in the

(Abrikossoff and Wulff[2])

The high positive correlation of multiple myeloma and chronic renal disease requires a pathogenetic consideration if possible based on a characteristic metabolic disturbance other than the proteinuria The creatinuria common in myeloma in this connection deserves no consideration The course in general pathology in many universities no doubt includes microscopic kidney slides from cases of myeloma for the demonstration of calcium metastases as first described by Virchow in osteomalacia and later in other conditions with extensive decalcification of the skeleton

About the mechanism by which calcium is eliminated through the kidney knowledge is wanting The authors had 1 case of multiple myeloma with most extensive decalcification like severe osteomalacia in which multiple spontaneous fractures were present The patient died before complete studies were made The following data are available The urine showed a definite trace to a heavy cloud of albumin no Bence-Jones protein was found repeated attempts to demonstrate it were unsuccessful On admission the urine showed a nephritic sediment Toward the end there was hyposteniuria The blood calcium on three different blood samples was 17 mg 16 9 mg and 20 mg per 100 cc serum Another myeloma patient with normal urine but with extensive decalcification presented a serum calcium of 12 2 mg The Rehberg test revealed a filtration rate of 63 cc per minute only (The plasma creatinine after the creatinine ingestion was 10 2 mg the concentration ratio was 66) Here therefore we have an instance of

definitely reduced filtration rate without albuminuria An even more marked instance is Case 5 This patient in two Rehberg tests two weeks apart had a filtration rate of 27 and 28 cc only (The corresponding plasma creatinine values were 9 9 mg both times and the concentration ratios 25 and 22) Ca e 7 had a serum calcium of 18 6 with a creatinine clearance of 32 cc per minute while another patient not otherwise discussed in this chapter had a serum calcium of 18 7 at the time his creatinine clearance was 20 cc per minute

These unquestionably severely damaged kidneys did not let through any plasma proteins as shown both by qualitative tests and by Fig 112 though in most of these cases Bence-Jones protein was eliminated in abundance Whatever may be the causative agent of the renal lesion in myeloma the process is expected pathogenet ically to differ from the ordinary chronic glomerulonephritis with its primary glomerular damage and its albuminuria

Though elevated blood calcium is not a constant finding in

metasta es

instance Paul

ley are not to

be confused with the extensive calcifications with different localiza

l

a

s

new chapter on pathology opened by Pfannenstiel in 1927 [23] still is largely unwritten it appears that the various pathological changes among which characteristic renal lesions constitute one can be explained on the basis of an altered and intensified calcium metab olism An extreme hypercalcemia occurs in the dog (Demole and Fromherz[8]) a change absent or less marked in the rabbit (Harris and Stewart[14]) In all experimental animals the kidneys show marked changes the primary basis for which are calcium depo its within the tubules in the interstitial tissue and al o though le s marked in the glomerular capsular space (Kreitmair and Hinzel mann [21] and Schmidtmann[27]) It is w rth noting that the changes so far described have been the results of experiments of short duration

Bell [4] in an extensive study of the pathology of the recorded ca es as well as of his own series concludes that the renal injury in multiple myeloma is due to obstruction of the tubules by casts Numerous other observers have recorded the presence of large numbers of casts in the tubules It is not certain however whether the casts are the cau e of the tubular degeneration or the effect

Bell implies the former interpretation and states that in his own series no casts were found in 2 cases (Cases 80 and 81) in which no Bence-Jones protein was excreted His Case 81 however is the same as the authors J B who showed a definitely lowered creatinine clearance (63 cc per minute), and demonstrates that the kidney injury may be independent of Bence-Jones proteinuria and casts

More recently, an even more striking case bearing upon the subject has been observed by one of the authors (Medes) The patient (Lankenau Hospital 107–34) was admitted about two months before death At that time only a very faint trace of albumin was found in his urine although his creatinine clearance test was reported as 5 5 his serum calcium 17 and his blood urea nitrogen 144 mg per 100 cc At necropsy a widespread myeloma was demonstrated The kidneys resembled those of the patient described by Perla and Hutner[31] The glomeruli were largely normal with some thickening and hyalinization of the basement membranes The tubules were markedly atrophic Large numbers of casts were present in which a considerable amount of calcium was demonstrated Calcium was also found in the walls of the tubules themselves No Bence-Jones protein was present in his urine

In view of these findings in experimental hypercalcemias and in multiple myeloma where the decalcification has been going on for years and sometimes reaches extreme degrees consideration should be given to the correlation of the frequently present renal disease with the increased calcium elimination rather than with the Bence Jones proteinuria

REFERENCES

1 ABDERHALDEN E 1919 Ein Fall von Bence-Jones scher Albuminurie Ztschr f physiol Chem 106, 130–132

2 ABRIKOSSOFF A AND WULFF F 1927 Ueber Eiweisskristallbildung in einem Fall von Myelom Verhandl d deutsch path Gesellsch 22 270 276

3 ALLARD E AND WEBER S 1906 Ueber die Beziehungen der Bence Jonesschen Albuminurie zum Eiweissstoffwechsel Deutsch med Wchnschr 32 1251 1252

4 BELL, E T 1933 Renal lesions associated with multiple myeloma Am J Path 9 393–419

5 BUSHKE F 1932 Uramie bei Bence-Jones scher Albuminurie Klin Wchnschr 11 408–410

6 COHN E J 1925 The physical chemistry of the proteins, Physiol Rev 5 349–437

A M 1925 Studies in

11 FOLIN, O, AND LOONEY, J M 1922 Colorimetric methods for the separate determination of tyrosine, tryptophane and cystine in proteins, J Biol Chem, 51, 421–434

12 GESCHICKTER, C F, AND COPELAND, M M 1928 Multiple myeloma, Arch Surg, 16, 807–863

13 GYORGY, P 1931 Umsatz der Erdalkalien (Ca, Mg) und der Phosphate, Handb norm u path Physiol, 16 (2) 1555–1641

the blood,

1147–1151

nd myelo

Jones pro-

Physiol,

42 163–200

18 JACOBSON, V C 1917 A case of multiple myeloma with chronic

27 MAINZER F 1932 Bence-Jonessche Proteinurie und Nierenfunktion, Ztschr f klin Med, 119, 363–380

28 MALENGREAU, F 1921 L'albumine de Bence Jones Arch internat d physiol, 18, 151–160

Tests for protein in urine,

myeloma clinical

multiple myeloma,

Am J Path, 6, 285–298

32 PERLZWEIG W A DELRUE G AND GESCHICKTER C 1928 Hyperproteinemia associated with multiple myelomas J Am Med Assn, 90, 755–757

33 PFANNENSTIEL, W 1927 Die Wirkung medizinischer Kohlepraparate auf Darmbakterien Klin Wchnschr, 6 2067

34 PUTSCHAR, W 1929 Ueber Vigantolschadigung der Niere bei einem Kinde, Ztschr f Kinderheilk, 48 269–281

35 REHSTEINER, K 1923 Eiweisskristalle in den Nieren, Centralbl f Path, 33 119–155

36 ROEHL, W 1905 Ueber Kalkablagerung und Ausscheidung in der Niere, Beitr z path Anat allg Path Suppl 7 pp 456–467

37 SCHMIDTMANN M 1929 Vigantolversuche Verhandl d deutsch path Gesellsch, 24 75–82

38 SVEDBERG T 1930 The pH-stability regions of the proteins Trans Faraday Soc, 26 740 744

39 SVEDBERG, T, AND SJOGREN B 1929 The molecular weight of Bence-Jones protein J Am Chem Soc 51, 3594

40 THANNHAUSER, S J, AND KRAUSS, E 1920 Ueber eine degenerative Erkrankung der Harnkanalchen (Nephrose) bei Bence-Jones scher Albuminurie mit Nierenschwund (kleine, glatte, weisse Niere), Deutsch Arch f klin Med, **133**, 183 192

41 TAYLOR, A E, MILLER, C W, AND SWEET, J E 1917 Studies in Bence-Jones proteinuria, II, J Biol Chem, **29**, 425–435

42 VAN SLYKE, D D 1911 The analysis of proteins by determination of the chemical groups characteristic of the different amino-acids, J Biol Chem, **10**, 15–55

[illegible]

Upsala Lakaref Forh, [illegible]

45 WALTERS, W 1921 Bence-Jones proteinuria, J Am Med Assn, **76**, 641–645

[illegible]

47 WILLHEIM, R 1927 Zur Frage der Eiweisskorper mit Bence-Jones scher Reaktion, Biochem Ztschr, **180**, 231 246

48 WILSON, D W 1923 A spontaneous crystallization of a Bence-Jones protein, J Biol Chem, **56**, 203–214

CHAPTER XXXII

SALTS AND EDEMA *

By A BAIRD HASTINGS PH D

Introduction —It is commonplace today to state that the problem of edema is intimately related to the problem of physiological regulation McLean[14] has made clear the importance of such a conception in his discussion of edema as a problem of volume regulation within the organism In viewing the problem as a whole it is not sufficient as he pointed out to consider simply the physico chemical influences involved the role of the nervous and chemical regulatory factors must be considered as well The application of the formulation known as the Gibbs Donnan equilibrium which describes equilibrium conditions between phases separated by preferentially permeable membranes can be of little aid in indicating causal factors of edema As in the case of all thermodynamic concepts this formulation is a statement of equilibrium states and gives no clue as to the path taken in reaching these states

This does not mean however that insofar as movements of electrolytes and water are influenced by ions incapable of passing limiting barriers changes toward the equilibrium states indicated by the Donnan formulation do not occur On the contrary any discussion of the relation of salts to edema must include an account of these influences and an estimate of their magnitude would be desirable

Without attempting to account for the physiological influences operating in the regulation of rates of absorption and excretion, this chapter will be an effort to discuss the problem *Given conditions in which there is salt accumulation in the organism or a change in reaction within the organism or both to what extent if any does our present knowledge of the movements of electrolytes and water account for the physiological effects observed?*

At the outset it should be stated that the time is not yet ripe for an adequate discussion of even this restricted section of the problem of edema However some data are now available and it may prove useful to attempt to apply them in an endeavor to point out where some of the gaps in our knowledge of electrolyte and water balance occur

* From the Lasker Foundation for Medical Research and the Department of Medicine the University of Chicago Chicago

FACTS CONCERNING SALTS AND EDEMA

Investigators in many countries have made experiments and clinical observations on the relation of salts to edema Among the names prominent in these studies are Magnus [15] Wahlgren [23] Magnus Levy [16] Wertheimer [24] Mond [17] Baird and Haldane [2] and Blum [4] Some have attempted to assign a causal relationship between salt retention and edema formation others have fixed their attention on the changes in acidity of the cells and their environment still others have looked to the change in balance between the osmotic and hydrostatic pressure factors for the clue to edema formation and control

A point which is an obvious corollary to the above considerations is that edema fluid can be formed only to the extent that salts and water are available for its formation The concentrations of the inorganic salts of edema fluids are with only slight differences practically equal to those of an ultrafiltrate of blood plasma It may be anticipated therefore that unless an adequate supply of certain salts is available edema fluid cannot be formed Since sodium chloride is quantitatively by far the most important inorganic constituent of body fluids it in turn becomes quantitatively the most important salt favoring the formation of edema

Man normally ingests and excretes approximately 3 to 6 gm of sodium chloride and 1 to 2 liters of water a day These amounts may be widely varied without the formation of edema And yet if the amount of salt ingested exceeds the amount which can be eliminated edema can be demonstrated even in the normal individual For example Baird and Haldane observed edema in a normal individual following the ingestion of 40 gm of sodium chloride In conditions where a so called tendency to edema is present the ingestion of much smaller amounts of salt is adequate for the development of edema On the other hand withholding salt and water in cases with a tendency to edema often serves to prevent its formation or if present to provide for its elimination In other words by denying the organism the two most essential constituents of edema fluid the formation of edema can in many instances be prevented

Of course it is never so simple as this in the actual clinical case A constant flow of fluids is an essential element of the life of cells and even if salts are withheld almost entirely the wasting of tissues provides a source of salts which can hardly be obviated

One may cite certain exaggerated experimental conditions which illustrate the role that the magnitude of available salt and water play in the development of edema For example it has been experimentally demonstrated by Ivy and his associates [3] that a nephrectomized dog will develop edema if salt and water are sup

plied in sufficient quantity This apparently never happens in normal dogs in spite of forcing salt and water by mouth.

A most complete and accurate study of the metabolism of various salts by a normal subject and a subject with nephrotic edema has been carried out by Loeb Atchley Richards Benedict and Driscoll [1] Their results may be summarized as follows

1 Sodium chloride when given by mouth was retained to some extent by both subjects however the retention was greater in the nephrotic patient than in the normal individual

2 Potassium chloride when administered behaved like a mildly acid salt More chloride was absorbed from the intestine than potassium and potassium was excreted faster than chloride Only a slight retention of this salt occurred however

3 When NH_4Cl was given the usual acidosis following administration of this salt resulted but no diuresis was observed

Throughout the study the normal subject and the nephrotic

Blum[4])

It should also be mentioned that the ingestion of sodium bicarbonate causes a retention of sodium and water Whether or not this is a result of the alkalosis produced or of the sodium ion is still a matter of discussion

The clinical observation that alkali salts such as sodium bicarbonate tend usually to increase edema and acid forming salts such as ammonium chloride and calcium chloride will often decrease edema led to a study of the water balance in patients with edema follc ork was carried out by ping Union Medical Coll edema and 1 with

of from four to eight days

It was found that although for the first day or so after giving sodium bicarbonate there was retention of water and an increase in edema this was not always maintained in spite of the continued administration of sodium bicarbonate The reverse occurred after giving ammonium chloride That is on the first day after the administration of ammonium chloride was begun there was an excessive loss of water Subsequently the loss of water above the intake was slight or within experimental error A brief period of increased excretion of water followed the cessation of the administration of sodium bicarbonate and increased retention of water

followed cessation of the administration of ammonium chloride These observations might be interpreted as providing direct quantitative proof that alkalosis favored water retention, and acidosis, water excretion

formation or present a new one Rather, an attempt will be made

this subject its objective will be attained

THE ELEMENTS OF THE SYSTEM

At the risk of simplifying the situation more than is legitimate, the biological system will be regarded as consisting of the following quantitatively important phases namely, the cellular elements of the blood the blood plasma the extracellular fluids and the cells of the tissues It would be idle to attempt a quantitative differentiation of the relative importance of the different tissues at this time Suffice it to say that the muscles and subcutaneous tissues are presumably those of greatest quantitative importance in effecting changes in water balance

The blood cells and plasma may be conceived as separated by a

through this membrane is also probably true The functional nature of the barrier between the tissue cells and the extracellular fluid is by no means clearly understood This is one of the fields in which more experimental data are needed It may be assumed, however that normally these membranes are also impermeable to proteins and cations By analogy with blood it might be supposed that cell membranes are permeable to H^+ Cl^-, HCO_3^- and other small anions This is not the case however, as will be subsequently pointed out Separating the blood stream and the extravascular ... a membrane freely

There exists in the capillaries a mean hydrostatic p... determined magnitude, and there is within the tissues a mechanical pressure of uncertain magnitude Such a simplified scheme as this is concerned solely with the thermodynamic factors of pressure

and ionic activity, and in no way minimizes the importance of such physiological factors as nervous and hormonal control, or rates of absorption and excretion

The System, Erythrocytes Plasma —The system, erythrocytes-

physico-chemical system has been made by Van Slyke and Henderson and their collaborators [6,22] As a result of their work the quantitatively important factors concerned with electrolyte and water distribution between plasma and erythrocytes have been found and related * The major changes occurring in electrolyte and water distribution when the oxygen and CO_2 tensions of the blood are altered have been satisfactorily accounted for by taking into account the fact that the erythrocytes behave as if provided with a membrane impermeable to bases and proteins and by postulating that at equilibrium there will exist (*a*) Equality of equivalents of positive and negative ions (*b*) osmotic equilibrium (*c*) distribution of diffusible ions satisfying the Gibbs-Donnan distribution law

Briefly these facts are as follows (*a*) In normal arterial blood at pH_s 7.4 there exists an unequal distribution of bicarbonate, chloride and hydrogen ions between plasma and erythrocytes Experiment has shown that the distribution may be expressed approximately by the ratios

$$\frac{(HCO_3)_c}{(HCO_3)_s} = 0.7 \qquad \frac{(Cl)_c}{(Cl)_s} = 0.61 \qquad \frac{(H^+)_s}{(H^+)_c} = 0.5$$

(*b*) The addition of carbon dioxide to blood has long been known to increase the bicarbonate concentration of both plasma and cells though the latter increases more than the former Furthermore the chloride concentration of the cells increases at the expense of the chloride concentration of the plasma These changes are ac

both the plasma and cells is lowered

2 At low pH there is less base bound by the proteins—in this case oxyhemoglobin This base though not capable of diffusing into the plasma is free to combine with chloride and bicarbonate ions which pass into the cells from the plasma

3 There is a redistribution of diffusible ions until the Gibbs-Donnan equilibrium is again established

4 Water passes from the plasma into the erythrocytes until osmotic equilibrium is restored

* The experimental work of these investigators was done on the system, erythrocytes-serum but there is reason to believe that the same relations hold for the system erythrocytes-plasma which is the physiological system discussed here

An additional experimental fact which further substantiates the above explanation is that oxygenation and reduction of blood at constant pH change the distribution of chloride bicarbonate and hydrogen ions in a similarly predictable manner

This brief summary of the effect produced by alteration in the reaction and degree of oxygenation of the blood has been introduced to illustrate how the distribution of water between serum and cells depends in part on non-diffusible protein ions

The System Plasma Extracellular Fluid —The situation in the system plasma-extracellular fluid requires more study than has yet been accorded it However several groups of investigators have made careful quantitative observations which may be mentioned Loeb Atchley and Palmer[11] have studied the system serum-edema fluid Hastings Salvesen Sendroy and Van Slyke[7] studied this system and other serum transudate systems both natural and artificial Pincus and Kramer[1] have studied ionic distribution between serum and cerebrospinal fluid Duke-Elder[5] has compared the concentrations of certain constituents of the aqueous and vitreous humors and blood serum Arnold and Mendel have made a comparison of the constituents of thoracic lymph and serum

From the earlier experiments it seemed that the unequal distribution of inorganic ions could be accounted for by assuming that the capillary wall was freely permeable to crystalloids and not to

hydrogen ions may be satisfactorily accounted for on the original

distribution of ions which leads to a distribution ratio of $\frac{(A)_s}{(A)_f} =$ 0 96 where $(A)_s$ stands for concentration of diffusible anions in the serum and $(A)_f$ the concentration in the protein free fluid The ionic distribution ratios found in Van Slyke s laboratory were

$$\frac{(HCO_3)_s}{(HCO_3)_f} = 0\ 96 \quad \frac{(Cl)_s}{(Cl)_f} = 0\ 97 \quad \frac{(Na)_f}{(Na)_s} = 0\ 91 \quad \frac{(H^+)_f}{(H^+)_s}\ \ 0\ 91$$

Potassium and calcium seem not to be distributed according to this simple hypothesis Whether this is due to permeability effects and calcium compounds in

to study the effect of alterations in pH on the system cellular fluid

From the plasma protein concentration and from the unequal distribution of ions between plasma and extracellular fluid Van Slyke has calculated that at normal pH and normal protein concentration the plasma will have an osmotic pressure of 25 mm of mercury in excess of that of the extracellular fluid Approximately four-fifths of this difference in osmotic pressure, or 20 mm Hg is due to the plasma proteins and one-fifth or 5 mm Hg is due to the Donnan equilibrium effect This means that at equilibrium a mean hydrostatic pressure of approximately 25 mm must exist in the blood stream to balance the osmotic pressure of the plasma

per liter are equal it is apparent that twice as much of the osmotic pressure of the plasma proteins is attributable to albumin as to globulin Therefore the reduction in plasma albumin which occurs clinically has a relatively greater effect in reducing the colloidal osmotic pressure of the plasma than the simple reduction in total protein concentration expressed as grams per liter would indicate It should also be noted that the difference in osmotic pressure between plasma and extracellular fluid due to the existing Gibbs Donnan equilibrium is of a relatively small order of magnitude and it is only this fraction of the plasma osmotic pressure which would be particularly sensitive to changes in ionic environment This matter has been well discussed by Fishberg[6] in a consideration of the relation of the serum proteins and lipoids to osmotic pressure The importance of plasma proteins in edema formation has been clearly proven by Leiter[7] and by Barker[8] by the production of

from blood plasma into tissue spaces and back into the blood stream is given in Fig 116 This diagram has with certain changes been drawn after that published by Schade and Claussen as modified by Peters and Van Slyke[10]

The first diagram illustrates the normal situation The hydrostatic pressure of the blood is indicated as falling in the capillary from about 40 mm Hg to 0 (The fall is probably not linear with distance) The colloidal osmotic pressure of the plasma is shown rising slightly as the blood traverses the capillary The result of these forces operating in opposite directions is the filtration of fluid, which occurs rapidly at first and then more slowly as the forces tend to become equal finally when the osmotic pressure exceeds the hydrostatic pressure the fluid is reabsorbed into the blood stream (In this description no attempt has been made to allow

An additional experimental fact which further substantiates the above explanation is that oxygenation and reduction of blood at constant pH change the distribution of chloride bicarbonate and hydrogen ions in a similarly predictable manner

This brief summary of the effect produced by alteration in the reaction and degree of oxygenation of the blood has been introduced to illustrate how the distribution of water between serum and cells depends in part on non-diffusible protein ions

The System Plasma Extracellular Fluid —The situation in the system plasma-extracellular fluid requires more study than has yet been accorded it However several groups of investigators have made careful quantitative observations which may be mentioned Loeb Atchley and Palmer[11] have studied the system serum-edema fluid Hastings Salvesen Sendroy and Van Slyke[7] studied this system and other serum transudate systems both natural and artificial Pincus and Kramer[1] have studied ionic distribution between serum and cerebrospinal fluid Duke-Elder[5] has compared the concentrations of certain constituents of the aqueous and vitreous humors and blood serum Arnold and Mendel[1] have made a [illegible]

capillary wall was freely permeable to crystalloids and not to substances of colloidal dimensions but more recent work seems to throw some doubt on this simple explanation However as a first approximation the distribution of chloride bicarbonate sodium and hydrogen ions may be satisfactorily accounted for on the original assumption that the capillary wall is normally impermeable to plasma albumin and globulin Further these proteins acting as anions on the alkaline side of their isoelectric point serve to establish an unequal distribution of ions which leads to a distribution ratio of $\frac{(A)_s}{(A)_f}$ = 0 96 where $(A)_s$ stands for concentration of diffusible anions in the serum and $(A)_f$ the concentration in the protein free fluid The ionic distribution ratios found in Van Slyke s laboratory were

$$\frac{(HCO_3)_s}{(HCO_3)_f} = 0\ 96 \quad \frac{(Cl)_s}{(Cl)_f} = 0\ 97 \quad \frac{(Na)_f}{(Na)_s} = 0\ 94 \quad \frac{(H^+)_f}{(H^+)_s} = 0\ 91$$

Potassium and calcium seem not to be distributed according to this simple hypothesis *Whether this is due to permeability effects* or the presence of complex potassium and calcium compounds in serum is not as yet known That a portion of the serum calcium is combined with proteins is known From the determinations now *available on the base bound by serum proteins* it should be possible to study the effect of alterations in pH on the system plasma-extra cellular fluid

From the plasma protein concentration and from the unequal distribution of ions between plasma and extracellular fluid, Van Slyke has calculated that at normal pH and normal protein concentration the plasma will have an osmotic pressure of 25 mm of mercury in excess of that of the extracellular fluid Approximately four fifths of this difference in osmotic pressure, or 20 mm Hg is due to the plasma proteins and one-fifth or 5 mm Hg is due to the Donnan equilibrium effect This means that at equilibrium a mean hydrostatic pressure of approximately 25 mm must exist in the blood stream to balance the osmotic pressure of the plasma [illegible]

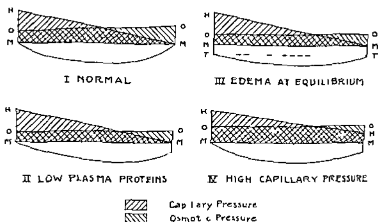
per liter are equal it is apparent that twice as much of the osmotic pressure of the plasma proteins is attributable to albumin as to globulin Therefore the reduction in plasma albumin which occurs clinically has a relatively greater effect in reducing the colloidal osmotic pressure of the plasma than the simple reduction in total protein concentration expressed as grams per liter would indicate It should also be noted that the difference in osmotic pressure between plasma and extracellul[illegible] Donnan equilibrium is of a re[illegible] *and it is only this fraction of* [illegible] would be particularly sensitive to changes in ionic environment This *matter has been well discussed by* Fishberg[6] *in a consideration* of the relation of the serum proteins and lipoids to osmotic pressure The importance of plasma proteins in edema formation has been clearly proven by Leiter[9] and by Barker[8] by the production of experimental edema in dogs following plasmapheresis

Pressure Forces and Movement of Fluid A diagrammatic representation of the forces which provide for the movement of fluid from blood plasma into tissue spaces and back into the blood stream is given in Fig 116 This diagram has with certain changes *been drawn after that published by* Schade and Claussen as modified by Peters and Van Slyke[20]

The first diagram illustrates the normal situation The hydrostatic pressure of the blood is indicated as falling in the capillary from about 40 mm Hg to 0 (The fall is probably not linear with distance) The colloidal osmotic pressure of the plasma is shown rising slightly as the blood traverses the capillary The result of these forces operating in opposite directions is the filtration of fluid, which occurs rapidly at first and then more slowly as the forces tend to become equal finally when the osmotic *pressure exceeds* the hydrostatic pressure the fluid is reabsorbed into the blood stream (In this description no attempt has been made to allow

for the amount of fluid which finds its way back into the circulation by way of the lymph channels)

The second diagram illustrates the situation when the net colloidal osmotic pressure of the plasma is lowered below normal This may be the result either of a lowered plasma protein concentration or of an altered permeability of the capillary membrane, so that some protein passes through it The hydrostatic pressure is here illustrated as remaining normal As a result of these unbalanced forces of filtration and reabsorption an excess of fluid will be left in the interstitial spaces, after the blood has traversed the capillary, which will continue to accumulate until equilibrium is again established



… hydrostatic pressure and …

from the *plasma* at various positions along the capillary

Such an equilibrium is illustrated in the third diagram The hydrostatic pressure and the colloidal osmotic pressure are those of the second diagram In addition the existence of a *hydrostatic* pressure of the fluid within the interstitial spaces by the area *M M–T T* has been indicated This will provide a back pressure *which will be added to the osmotic* pressure of the plasma proteins … pressure of the plasma in the capil-

…rces will be the filtration of some

…absorption of an equal amount

…be considered to *be in a state of* equilibrium until some change occurs in the forces which will provide for its increase or its reabsorption

Such a change might conceivably be brought about by 1 An increase in the net colloidal osmotic pressure of the plasma

2 A decrease in the hydrostatic pressure of the blood in the capillaries

3 An increase in the back tissue pressure

Presumably the first named is the change which usually takes place but since it does not always occur clinically with the elimination of edema the other possibilities should be considered

Finally in the fourth diagram there is illustrated the usually accepted mechanism of the formation of cardiac edema The hydro-

plasma is represented as normal The net result of this disturbance of forces would be to provide for an excess of fluid filtered over that reabsorbed

These then are the primary forces conceivably operating in the formation of edema Furthermore since they are the forces normally operating in fluid exchange changes in their magnitude alone would account for most of the abnormalities observed

EFFECT OF CHANGING pH IN VIVO ON THE ELECTROLYTE-WATER EQUILIBRIUM

The experiments on the blood previously referred to on the effect of changing the pH of the system erythrocytes plasma were limited to *in vitro* experiments It was of interest to know whether the conclusions reached concerning electrolyte and water distribution by experiments *in vitro* are equally applicable to conditions *in vivo* To determine this H N Harkins and the author have performed a series of experiments on the electrolyte and water distribution in

found in these experiments that the distribution ratio of chloride

by its action on the blood and since it was found not to be excreted in the course of the experiments it was supposed that similar adjustments took place between the tissue cells and the extracellular fluid

Experiments have also been performed in which experimental alkalosis was produced in animals by sodium carbonate These

experiments led to changes of an opposite nature The distribution ratios of chloride and bicarbonate between erythrocytes and plasma were decreased instead of increased There was correspondingly a passage of water from erythrocytes to the plasma Since tissue *analyses were not made we have no knowledge of the effect which* the alkalosis had outside of the blood stream There was of course in these experiments a marked diuresis

ELECTROLYTE AND WATER DISTRIBUTION FOLLOWING THE ADDITION OF NaCl TO BLOOD IN VITRO

If the conclusions reached by Van Slyke Wu and McLean con

distribution

be possible

NaCl *in iso*

tonic aqueous solution and (2) making plasma hypertonic with NaCl alone Experiments to test whether the predicted changes are actually realized have been performed by Morgan [18] in L J Henderson s laboratory and by Van Dyke and the author

1 The addition of NaCl in isotonic solution caused an increase in chloride and a decrease in HCO_3 concentration within the serum phase If the pH of the serum was kept constant however there was a redistribution of the chloride and bicarbonate ions until

condition the magnitude of the plasma phase may be increased without a change of significant magnitude in the water or electrolyte distribution

2 Making serum hypertonic with NaCl did however influence the electrolyte and water distribution There was an increase in

mented the effect

ythro

loride

making the plasma hypertonic caused a lower distribution ratio of chloride and bicarbonate between erythrocytes and plasma There *also occurred a passage of water to the plasma to restore osmotic* equilibrium

CHARACTERISTICS OF THE SYSTEM TISSUE-EXTRACELLULAR FLUID

From a physico chemical standpoint the most important difference between the systems, tissue tissue fluid and erythrocytes plasma is that of the permeability of the membranes separating the phases Both blood and tissue cells are impermeable to cations and proteins

but whereas the former are freely permeable to chloride the latter (or at least those of striated muscle) are apparently impermeable to this ion Peters[19] has pointed out that such a conclusion is compatible with certain available knowledge concerning this system and we have reached a similar conclusion from data obtained by L Eichelberger and the author For example muscle removed from the normal living organism was found to have a chloride concentration of only 20 millimols per kg of tissue even on a water basis this amounted to only 28 millimols per kg of water The chloride concentration of blood plasma lymph and edema fluid amounts to approximately 100 millimols per kg of water If one *assumes that 20 per cent of the bulk of muscle analyzed is extra*cellular fluid whose composition corresponds to that of edema fluid all of the chloride found in the muscle is accounted for Similarly, in the case of sodium muscle was found to have 31 millimols per kg of tissue whereas edema fluid had 145 millimols per kg If one assumes that 21 per cent of the muscle is extracellular fluid all of the sodium is thereby accounted for The muscle cells contain also approximately 160 millimols per kg of water—largely potassium—to which the cells are normally impermeable

When muscle is removed from an animal and equilibrated *in vitro* with the serum of the same animal under the most favorable conditions of pH and temperature the permeability relationships change radically When equilibrium is established it is found that the chloride concentration has risen from 28 to 72 millimols per kg of water Under these conditions a change in pH causes a shift in the chloride distribution between muscle and serum in a direc-

i i vitro and *in vivo*

tem erythrocytes plasma

EFFECT OF pH ON THE SYSTEM MUSCLE-EXTRACELLULAR FLUID

In order to test whether the Gibbs Donnan distribution law accounted for the changes produced in the system muscle-extracellular fluid when the reaction and salt content of the organism were altered the following experiments were performed

Specimens of muscle from anesthetized dogs were removed from

one side of the animal and blood was drawn simultaneously A carbon dioxide acidosis was then produced in the animals by causing them to rebreathe in a closed system until the blood pH fell to between 7 0 and 7 1 Muscle from the other side and blood were then again removed for analysis of their sodium chloride and water concentrations It was found that both the sodium and chloride decreased by comparable amounts This could be satisfactorily accounted for by the assumption that there had been a decrease of between 15 and 20 cc of extracellular fluid per kg of muscle Such a result could hardly be the consequence of the Gibbs Donnan equilibrium law but rather the intervention of physiological processes It is of interest however to point out in this connection that these experiments constitute direct evidence for the generally recognized observation that acidosis tends to diminish edema

The experiments just cited are concerned with the effect of pH changes on the distribution of water and salts in the organism without the addition of material capable of being used for edema fluid Furthermore if the above interpretations of our experimental results are correct an analytical method of estimating quantitatively the extent of edema is suggested namely that by sodium and chloride analyses of tissue impermeable to these ions an estimate of the amount of extracellular fluid per kilogram of tissue may be made

From the foregoing it may be seen that the direct application of the Gibbs Donnan distribution law does not account for the changes in water and salts in the system muscle-extracellular fluid as affected by pH However the following considerations should not be overlooked When the pH of the plasma is lowered by carbon dioxide there is as we have stated a lower pH within the red cells and subsequent movement of chlorides and water into the cells This results in slightly raising the colloidal osmotic pressure of the plasma which in turn would tend to draw fluid from the extracellular space until equilibrium was again restored Whether this is a quantitatively important factor cannot be definitely stated at present

EFFECT OF NaCl ON THE SYSTEM MUSCLE-EXTRACELLULAR FLUID

When 1 liter of isotonic NaCl solution was injected intravenously instead of changing the pH it was found that the estimated *increase* in extracellular fluid of muscle was approximately 20 cc per kg This provides direct evidence that when the volume regulation of the organism is disturbed by the sudden acquisition of potential edema fluid its presence in tissues may be demonstrated even in dogs which do not show palpable edema from sodium chloride alone

When sodium bromide was given to dogs by mouth well marked edema developed in most animals Since bromides are not as easily excreted as chlorides we interpret the production of a salt edema in this case as an instance of providing the organism with more potential edema fluid in a given time than could be eliminated

essential quantitative relations between the proteins and the inorganic constituents of the various phases of the normal organism and in addition their relative bulk The former is shown by the height along the ordinate the latter by extension along the abscissa

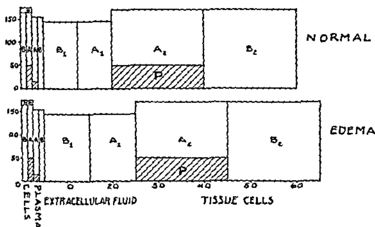


FIG 117 —A chart to illustrate the relations of water and electrolytes of erythrocytes plasma, extracellular fluid and tissue cells under normal conditions and after the addition of 5 kg of edema fluid

The four essential phases are indicated here as blood cells blood plasma extracellular fluid and tissue cells Equivalent ionic equality is indicated by equal heights of the blocks representing equivalent amounts of anions and cations in each phase Osmotic equality is indicated by equal total heights of the unshaded areas representing cations and anions in each phase The existence of a Gibbs Donnan equilibrium where it has been shown to apply (i e between cells and plasma and between plasma and extracellular fluid) is indicated by the relative heights of the anion areas for cells and plasma and by the heights of the anion and cation areas for plasma and extracellular fluid

The lower chart which represents the edematous condition is in

all respects similar to that of the upper chart save in two essential respects

1 The plasma protein concentration is lower and the base bound by the plasma proteins is proportionately decreased

2 The magnitude of the extracellular fluid phase is increased

This chart is presented in order to emphasize again the fact that the volume of one phase may be markedly altered without essentially changing the ionic or osmotic relationships in the other phases

Conclusions —1 Edema is an exaggerated condition of the normal process of filtration of fluid from the blood plasma through the capillaries

2 Its formation is favored by a condition of alkalosis and alkalinizing salts

3 Its formation is impeded by a condition of acidosis and acidifying salts

4 The Gibbs Donnan distribution law does not aid directly in accounting for the changes in edema accompanying acidosis and alkalosis.

5 The role of sodium chloride is passive Even when factors are favorable for edema formation it can occur only to the extent that salt and water are available It is suggested that direct analysis of tissues for sodium chloride and water provides a means of quantitatively studying the extent of edema in experimental animals

The important questions of how hydration of the proteins influences water movement within the organism and how changes in reaction and the concentration of ions in the environment influence the degree of hydration have not been dealt with in this discussion That they must ultimately be taken into account in any complete description of the relation of salts to edema is of course appreciated

REFERENCES

1 ARNOLD R M AND MENDEL, L B 1927 Interrelationships between the chemical composition of the blood and lymph of dogs J Biol Chem 72 189–211

S 19?2 Salt and water elimination

1930 Experimental edema (nephro al origin in patients Arch Int Med

4? 519–540

4 BLUM, L AND VAN CAULAERT 1925 La composition du sang dans la rétention chlorurée sèche Compt rend Soc biol 93 283 285

5 DUKE ELDER, S 1927 Biochemistry of aqueous humor Biochem J 21 66–77

8 701–711

8 HENDERSON L J 19?8 Blood a study in general physiology New Haven Yale University Press

9 Leiter L 1928 Experimental edema, Proc Soc Exp Biol and Med, 26 173 175

10 Hastings A B, Lu, S H, and Dievaide F R 1931 Studies of acid-base and water balance in edema J Clin Invest, 10 683

11 Loeb, R F, Atchley D W and Palmer W W 1921 On the equilibrium condition between blood serum and serous cavity fluids J Gen Physiol, 4 591 595

12 Loeb R F Atchley D W, Richards, D W Jr Benedict E M, and Driscoll, M E 1932 On the mechanism of nephrotic edema J Clin Invest, 11 621–639

13 Lyon, E E Shafton A L and Ivy A C 1929 Prolongation of the life of nephrectomized dogs, Arch Int Med 44 424–437

14 McLean F C 1925 Edema as a problem in physiological regulation Physiol Rev 5 618–640

15 Magnus R 1900 Ueber die Veranderung der Blutzusammensetzung nach Kochsalzinfusion und ihre Beziehung zur Diurese Arch exp Path u Pharm, 44 68–126

16 Magnus-Levy, A 1921 Natriumbikarbonat und Kochsalzodeme Ztschr f klin Med 90 287 293

17 Mond R 1924 Untersuchungen am isolierten Dunndarm des Frosches, Arch f d ges Physiol 206 172 193

18 Morgan, W P Personal communication to the author

19 Peters J P 1933 The distribution and movement of water and solutes in the human body Yale J Biol and Med 5 431–467

20 Peters, J P and Van Slyke D D 1931 Quantitative clinical chemistry, Baltimore Williams & Wilkins Company 1 (Interpretations) 658

21 Pincus, J B and Kramer B 1923 Comparative study of the concentration of various anions and cations in cerebrospinal fluid and serum J Biol Chem, 57 563–470

22 Van Slyke D D 1926 Factors affecting the distribution of electrolytes water and gases in the animal body Monographs on Experimental Biology, Philadelphia J B Lippincott Company

23 Wahlgren V 1909 Ueber die Bedeutung der Gewebe als Chlordepots, Arch f exp Path u Pharm 61 97–112

24 Wertheimer, E 1925 Weitere Untersuchungen an lebenden Membranen Arch f d ges Physiol 210 527–544

CHAPTFR XXXIII

EDEMA IN DOGS FOLLOWING SODIUM BROMIDE ADMINISTRATION *

By A BAIRD HASTINGS PH D

AND

H B VAN DYKE PH D M D

BROMIDE EDEMA

WHILE the production of experimental edema in normal dogs by NaCl administration by mouth unaccompanied by other procedures has not been observed as far as the authors are aware it has been found that the closely related salt sodium bromide will produce a well marked edema in most dogs The sodium bromide must be given in fairly large doses 1 to 2 gm per kilo per day accompanied by an adequate supply of water The edema may appear on the second day but usually is not marked until the fourth or fifth day following the initial administration of the salt It is always present in the extremities and frequently in the tissues around the head and scrotum Ascites however has never been observed Increase in size of the extremities increase in weight and a shortened disappearance time of the wheal produced by intracutaneous injections of NaCl or NaBr accompany the edema

In the hope of detecting with greater accuracy the time of onset of water retention the technique used by Newburgh in his studies of water balance on patients was adapted for use with dogs A scale was used upon which the dogs could be weighed with an accuracy of 5 gm each day The water and food intake and the water and feces output were measured The water content of the food and feces was also determined From these data the water balance for twenty four hour periods could be estimated

Using this technique it was possible to follow the change in water balance with greater accuracy For example a positive water balance amounting to 500 to 750 gm of water was found present usually about the third day after the administration of sodium bromide was begun At this stage palpable edema and a shortened disappearance time of the wheal produced by both NaCl and NaBr

* From the Lasker Foundat on for Med cal Research and the Department of Med c ne and the Department of Phys ological Chemistry and Pharmacology of the Un ersity of Chicago

injected intracutaneously were noted A gain in weight and water retention appeared before the edema was palpable A loss of weight but not a corresponding loss of water usually occurred as the result of failure of the animals to eat food after three days of bromide administration The edema often was even more marked at this time It is noteworthy that the administration of NaCl seemed to accelerate the disappearance of the edema The incidence and extent of the edema observed in a series of dogs are given in Table 79

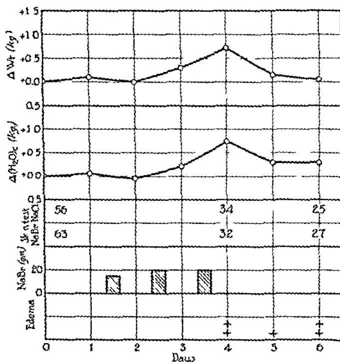


FIG 118 —The changes in weight and water balance occurring in a dog given sodium bromide by mouth The disappearance-time of the wheal produced by the intracutaneous injection of salt is indicated in minutes

The fact that edema was produced in many but not all dogs (13 out of the 17 used developed edema) suggests that a tendency to edema is characteristic of this species as well as of man That the edema was not merely incidental to the depression produced by the bromides is shown by the fact that dogs previously showing edema upon bromide administration failed to develop it when kept in a comparable state of depression by barbital and given large

amounts of NaCl and water In view of these results it is of course remarkable that edema is not encountered in man upon bromide administration It is possible that determinations of the water balance of patients on bromide therapy might at times reveal water retention

TABLE 79 —INCIDENCE AND EXTENT OF EDEMA IN DOGS STUDIED

Dog No	Medication		Day of first appearance of edema after bromide feeding begun	Duration of edema days	Thickening of skin	Pitting on pressure			Swelling of scrotum	Day of death after bromide-feeding begun	Cause of death
	NaCl	NaBr				*Fore-legs*	*Hind legs*	Breast			
3A	+	+	6	4	+	+	+		+	Alive	
B	0	+	8	3	+	+	+				
C	+	+	3	7	+	+	+	+	+		
4	+	+	6	3	+	+	+			Alive	
7	+	+	6		+	+	+			9	Bronchopneumonia
9	+	+	3	8	+	+	+			11	Bronchopneumonia
10	0	+	7	3	+	+	+			15	Killed
11	+	+			0	0	0	0	0	5	
12	0	+	4	3	+	+	+		+	Alive	
13	0	+	4	3	+	+	+		+	Alive	
14	0	+	5	4	+	+				Alive	
15	0	+			0	0	0	0	0		
18	0	+			0	0	0	0	0		
19	0	+	5	3	+	+	+	0	+	Alive	
20	0	+			0	0	0	0	0	Alive	
21	0	+		3	+	+	+	0	0	Alive	
22	0	+	3	2	+	+	+	0	0	Alive	
23	0	+	2	2	+	0	0	0	0	4	Bronchopneumonia
24	0	+	3	4	+	+	+	0	+	Alive	

Electrolyte and Water Changes in Bromide Edema —*Chemical* studies of the blood have revealed the following changes following *NaBr administration The total halide concentration of the serum* rose as did that of the erythrocytes the bicarbonate and pH *showed no particular change Of great* interest from the stand point of ionic distribution is the fact that soon after bromide ad ministration the bromide concentration in the cells rose to a value in excess of that expected from the application of the Van Slyke Wu and McLean equations —in fact in some instances twice as much bromide has been found in the cells as in the serum whereas 0 7 as much was anticipated [1] This occurred at the expense of the chloride concentration of the cells The total halide *distribution* ratio remained normal The only explanation offered for this phenomenon is that a portion *of the bromides may displace chlo-* rides from chemical combination within the cells

No satisfactory explanation for the edema encountered in dogs after sodium bromide administration has been found All that we

may say at the present time is that given a situation in which the rate of NaBr absorption exceeds the rate of NaBr excretion certain electrolyte and water changes may be expected The increased cation concentration in the plasma leads to a lowered total halide ratio and water passes from blood cells to plasma to restore osmotic equilibrium This would bring about a lower plasma protein concentration leading to a disturbance in the balance between hydrostatic pressure and osmotic pressure Concomitantly there will tend to be passage of water and salts from the plasma phase to the extracellular fluid phase until equilibrium is again established Due to the increased concentration of base and electrolyte in the extracellular fluid a redistribution of anions and water between the tissue

NaBr administration

Effect of Acidosis on Bromide Edema —In experiments in which an acidosis was produced in dogs by both NH_4Br and NH_4Cl followed by NaBr administration we have not observed any palpable edema Under conditions of acidosis a higher distribution ratio of both bromides and chlorides between serum and cells was found than when the acid base balance was normal This is in harmony with the distribution changes predicted by the Van Slyke Wu and McLean equations

Reasoning as in the case of the relation of acidosis to NaCl edema the following changes may be pictured as having occurred The acidosis led to a diminution in the amount of base bound by the serum and blood cell proteins This in turn led to an increase in the distribution ratio of chloride and bicarbonate between the cells and serum and to the subsequent passage of water from the serum into the cells In the case of the system tissue cells-extra

fluid phase

Effect of Alkalosis on Bromide Edema —A comparison has been

mide fed was excreted under normal conditions only 35 per cent was excreted in the same time (about eight days) under conditions of alkalosis It is felt that these experiments may throw some light on the question of why edema is more apt to occur following salt administration under conditions of alkalosis than when the acid base balance is normal

The water balance in dogs with alkalosis following intensive sodium bromide administration has not yet been carefully studied

Conclusion — 1 The administration of sodium bromide by mouth to dogs leads to a generalized edema without ascites

2 Measurements of water balance indicate that there is water retention prior to the appearance of palpable edema

3 The influence of experimental acidosis and alkalosis on bromide edema is discussed

References

[illegible] B 1931 Stud es of bromide dision of bromides and chlorides in the tration of sodium bromide J Biol

2 VAN SLYKE, D D WU H, AND McLEAN F C 1923 Studies of gas and electrolyte equilibria in the blood V Factors controlling the electrolyte and water distribution in the blood J Biol Chem 56 765-849

CHAPTER XXXIV

RECENT DANISH WORK ON EDEMA

By POUL BRANDT REHBERG Ph D

Introduction Albuminuria —In practically all diseases of the kidneys, albuminuria is one of the symptoms The loss of protein is usually associated with pathological processes in the kidney itself, but may occur even when no lesion of the kidney can be demonstrated (orthostatic albuminuria) What is the origin of this protein?

When inflammation or degeneration is going on in the glomeruli these processes may give rise to destruction of cells, the protein content of which may be expelled into the tubules along with disintegrating leukocytes and thus give rise to albuminuria Most of the urinary protein has however another origin—from serum proteins excreted through the glomeruli That this is so, may be inferred from various circumstances It is often possible to demonstrate albumin in the glomerular capsule and the proteins present in the urine can in no way be distinguished from those of blood Geill,[2] of the Rigshospital, in Copenhagen gives the result of a series of experiments on the physico-chemical properties of the proteins of both blood and urine His results are that their behavior toward precipitation with ammonium sulphate is the same and that the precipitation is influenced in the same way by hydrogen-ion concentration and the concentration of the protein He moreover, confirms the result of previous authors—that most of the excreted protein is serum albumin and that only in cases of amyloidosis the amount of globulins is considerably increased, sometimes exceeding the amount of albumin excreted This is an additional reason for distinguishing sharply between nephroses and amyloidoses As an indication that the origin of urinary protein is in the blood we may also take the fact that a considerable protein excretion is always followed by a fall in the protein content of the blood

Bing[1] has demonstrated that the concentration of albumin in the urine in nephritis is proportional to the concentration index This would be very difficult to understand if creatinine and albumin were not excreted by the same process, *viz*, filtration of the glomeruli It further means that in evaluating the excretion of albumin, emphasis should be put not on the concentration but on the absolute amount excreted

The reason for the excretion of protein is of course clear when the glomeruli are damaged to such an extent that the changes can be demonstrated histologically. When the epithelium in glomerular nephritis is highly altered, the glomerular capillaries partly coalesced, partly injured so that blood corpuscles may pass through the wall, it is no wonder that albumin may also pass through. And that albuminuria may arise through stasis is also understandable when we consider how dependent the capillaries are on the blood flow, how rapidly they answer to a reduction in their blood supply by dilatation and increased permeability.

Much more difficult to understand is the albuminuria of nephroses and those are just the cases where the excretion of albumin is most prominent. Here we have no disturbance of the blood flow, and damage to the glomeruli is usually absent or when demonstrable is only slight. It is tempting to seek the cause of the changed permeability not in the epithelium itself but in the composition of the blood flowing through the glomeruli.

It is becoming more and more common to regard nephroses not as a local kidney disease, but to see in the changes of the kidney function only a symptom of an underlying general disease with disturbances in the lipoid system of the organism—an almost constant finding is cholesterinemia. Rusznyak and Nemeth[16] have shown that a kidney perfused with a fluid containing serum protein will excrete protein if saponin is added to the perfusion fluid, and that the excretion is stopped when a saponin free, calcium rich perfusion fluid is later used. The same has been shown by other authors to hold for ultrafilters. We may perhaps hope to find an explanation for the albuminuria of nephroses in a similar mechanism. The albuminuria leads, as already said, to a lowering of the protein content of the blood, and in this lowering we see, like Epstein,[2] the cause for the edema.

EDEMA

Types of Edema.—By edema we understand an abnormal retention of water in the body outside the circulatory system. When we define edema in this way we have to distinguish sharply between two different edemas, intracellular and intercellular. If the water is retained intracellularly because of disturbed metabolism of the cells we shall only be able to demonstrate an edema by a gain in weight and swelling of the limbs, but we know very little about the extent to which this really occurs. Large amounts of water may no doubt be present in the intercellular spaces producing a swelling but not making itself manifest as water—an intercellular edema. In edema may in this way be taken for an intracellular edema. In standing quietly in an upright position 300 to 400 cc. of water may be filtered into the feet and the lower part of the legs without

producing any symptoms beside swelling The existence of true intracellular edema can be regarded as established, but so far we know nothing about its mechanism Intercellular edema is much better known and it is the pathogenesis of this we shall discuss here *

Factors Conditioning Intercellular Edema —The Danish work on this problem arose out of the study of the physiology of capillaries carried on by Krogh [9] Concluding from Starling's[17] classical work on absorption of fluids that it was the equilibrium between the hydrostatic pressure in the capillaries and the colloid osmotic pressure in the blood which determined the direction of water movement through the capillary walls Krogh undertook a study of these two factors

For the study of the colloid osmotic pressure two micromethods were developed with which it is possible to determine in about six hours the osmotic pressure of plasma with an accuracy of plus or minus 5 cm H_2O and using less than 1 cc of plasma for the determination

The results with regard to the colloid osmotic pressure may be summarized as follows The normal colloid osmotic pressure of human blood is on an average 380 mm Fibrinogen exerts no measurable pressure Plasma and serum give the same value The fraction of protein with the smallest molecule is responsible for a large part of the pressure As soon as a membrane is not completely tight to protein there is a large drop in the pressure measured

The results with regard to the capillary pressure were that capillary pressure depended on two factors (1) The friction to be overcome on the way back to the heart and (2) the pressure of the venous blood column from the heart to the place where the measurement is made The latter factor is the dominating one as soon as we deal with regions lying below the heart since that part of the pressure which is due to the friction in the vessels is less than 10 cm of water The part played in the capillary pressure by the hydrostatic pressure of the blood column is however very variable depending on the muscular movements of the subject and the efficiency of his vein valves

CLINICAL STUDIES OF EDEMA

Nephrotic Edema —The plan of Krogh was now to study the balance between colloid osmotic pressure and capillary pressure under different circumstances and among other things it was planned to study also clinical cases showing edema One of the

* Only the Danish work or work directly connected with it is reviewed here Further information on the subject may be found especially in Gowaertz [4] important papers and in Meyer's [3] review

first cases which were examined by Hagedorn, Rasmussen and the author[5] in 1922 was a patient with pure nephrosis He had considerable edema of the legs and large amounts of ascitic fluid, so that several liters could be emptied at intervals of a few days His urine showed an albuminuria varying between 2 and 3 per cent His blood showed a protein content of 5 per cent against the normal 7 5 to 8 per cent When we determined the colloid osmotic pressure of the blood we found, however, that this was only 100 mm of water against the normal 350 to 400 This reduction in colloid osmotic pressure was far greater than could be

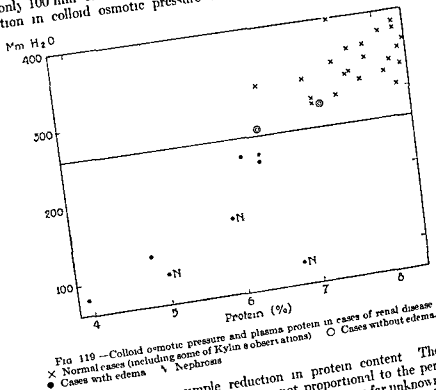


FIG 119 —Colloid osmotic pressure and plasma protein in cases of renal disease × Normal cases (including some of Kylin's observations) ○ Cases without edema. ● Cases with edema N Nephrosis

accounted for by a simple reduction in protein content The colloid osmotic pressure of protein is not proportional to the percentage of protein in solution, but varies for reasons so far unknown, in such a way that the pressure per per cent of protein—the specific osmotic pressure we call it—is higher, the greater the protein concentration is At a protein concentration of 5 per cent the specific osmotic pressure should be about 37 mm water against a pressure of about 46 mm per cent at the normal protein concentration of plasma (Fig 119)

The 5 per cent protein found in the blood of the nephrotic patient should therefore, exert a pressure of 185 mm, whereas it actually

exerted only 100 mm This indicated that besides a mere quantitative reduction in concentration the proteins of the blood had been changed so that the remaining molecules had less osmotic activity We now studied the urine A sample of urine with a protein percentage of 2 8 showed a colloid osmotic pressure of 240 mm This was three times as high a specific pressure as a blood with this protein content would show and from this we drew the conclusion that the cause of the edema was to be looked for in the following successive events

The primary change is that the glomeruli for some unknown reason become abnormally permeable but only so much that the smallest and therefore most active protein molecules are filtered out As a result of this the protein content of the blood is lowered and changed in such a way that a large reduction in the colloid osmotic pressure results and with this reduced to 100 mm of water the capillary pressure will be higher than the osmotic pressure in most places in the body especially in the lower part and in the portal system Water will be filtered out and edema results As the loss of protein was up to 20 gm a day or about one seventh of the patient's total amount of plasma protein and as he showed no sign of nitrogen retention we replaced the protein poor diet with a protein rich one

Following this case which was reported briefly in the first edition of Krogh's book on capillaries a number of cases have been studied by Krogh's co-workers all showing the same type of lowering of colloid osmotic pressure though generally not so pronounced Several investigators have published papers confirming the results but the author will discuss only the results obtained by Iversen and Nakazawa with various co-workers [6 7 8 11]

In a case of nephrosis they found a pressure of only 89 mm of water with a protein content of 6 77 per cent which ought to have given 290 mm pressure that is it gave only one-third of what was expected The urine contained 1 65 per cent protein with a pressure of 185 mm (instead of 45 mm) In this case it is even more evident that the smaller active molecules had been excreted Iversen and co-workers studied a number of cases of edema associated with kidney diseases and found that whether it is acute nephritis chronic nephritis or nephrosis edema does not occur until the colloid osmotic pressure of the blood is lowered to about 250 mm of water The material of Iversen and Nakazawa moreover gives the very important information that while the specific osmotic pressure of the plasma colloids decreases when the plasma is diluted the specific osmotic pressure of the urine proteins is higher the smaller is the protein percentage This means that the smaller the percentage of protein in the urine the smaller are also the molecules excreted

This is eviden
permeability of
conclusions drav
and we may regard it as proved that in kidney cases edema is due to a lowering of the colloid osmotic pressure of the blood In no case is it necessary to assume any damage to the capillaries since the edema fluid shows only a small amount of protein with a neglgible osmotic pressure

Iversen and Nakazawa studied next the pathogenesis of edema in other diseases

Cardiac Edema The question was whether the explanation here given would hold also for other forms of edema Could a lowering of the colloid osmotic pressure of the blood be demonstrated—and was an eventual lowering sufficient to explain the formation of the edema?

A number of patients with cardiac edema were examined first

on the basis of this lowering alone but in other instances the lowering though distinct was hardly sufficient to explain the formation of edema In 1 case for instance on different occasions on

unchanged as the pressure gradually fell to 26 mm

There is a distinct relation between the colloid osmotic pressure

in these patients The capillary blood pressure is in many cases increased because the venous return to the heart is insufficient and moreover the capillary walls are injured through the stasis and may be abnormally permeable The edema fluid of cardiac patients generally contains about 1 per cent protein whereas in nephrotic edema its value is always below 0 5 per cent The explanation of the edema in cardiac patients *is therefore to be* found in a combination of the following causes decreased colloid osmotic pressure of *the blood increased capillary blood pressure* and to some degree increased permeability of the capillary walls

Iversen discusses the cause of the decrease in the protein content of the blood of cardiac patients In the few cases in which the *degree of albuminuria was large enough* to allow a determination of the colloid osmotic pressure of the urine it came out that here

also the small protein molecules were the ones preferentially excreted. The amount excreted is however usually small and though the loss of protein may go on for months it is hardly possible that this loss together with the small amounts found in the edema can explain the lowering unless the regeneration of the protein is in some way disturbed. As an example which points toward this possibility Iversen records the following case.

The patient suffered from high grade insufficiency of the heart; he had albuminuria and very considerable edema. On November 5 his blood showed 4.81 per cent protein with a colloid osmotic pressure of 173 (specific spressure 36). During treatment the albuminuria stopped and from November 23 to December 21 his

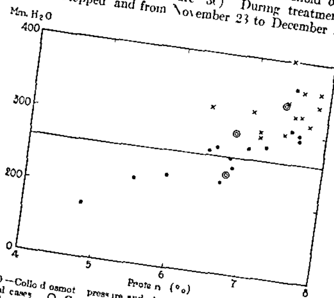


Fig. 10.—Colloid osmotic pressure and plasma protein in cases of heart disease. × Normal cases. ○ Cases without edema. ● Cases with edema. The line indicates the limit below which edema occurs in renal diseases. (See Fig. 119.)

urine was free from albumin. His blood proteins during this period increased to values varying around 6 per cent or even higher. However as late as December 6 when the protein percentage was 6.77 the colloid osmotic pressure was only about 240 mm. This gives a specific pressure of 35 mm. against a normal value of 43, which shows that the restoration of the protein content was due chiefly to formation of larger molecules. Iversen seeks the reason for this failure to renew the smaller protein molecules in the stasis of the liver.

In a case of orthostatic albuminuria the pressure of the blood colloids was on the other hand quite normal showing that here the formation of protein could compensate for the excretion.

Iversen now proceeded to study other forms of abnormal fluid collections in the body. This work will be mentioned also because the results obtained confirm the whole view.

Ascites.—Iversen maintains that the ascites combined with stasis of the liver and tuberculous ascites are of quite different origin. When a protein rich fluid is formed outside the capillary system the equilibrium becomes seriously disturbed. In the abdominal cavity we have then as forces trying to drive water out of the capillaries the capillary blood pressure (P_c) and colloid osmotic pressure of the protein-containing fluid outside ($C.O.P._o$). As forces trying to drive water into the blood we have the colloid osmotic pressure of the blood ($C.O.P._b$) and the hydrostatic pressure of the fluid outside (P_o).

As long as $P_c + C.O.P._o = P_o + C.O.P._b$ no movement of water will take place but if the two former forces P_c and $C.O.P._o$ are increased so that their combined pressure is higher than that of the other two fluid will be pressed out and ascites formed. Of these four pressures we can measure the two arising from the colloids and we can measure the pressure under which the fluid in the abdominal cavity stands. We cannot measure the capillary pressure but we can maintain that normally it must be very low as one can see cases with a colloid osmotic pressure of the blood of only 100 mm. of water without any formation of edema. The factor which changes most is the colloid osmotic pressure of the ascites fluid. In a series of 12 cases Iversen finds values between 25 and 264 mm. so that 2 cases of hepatic cirrhosis gave values respectively of 25 and 29 mm. of water, while the colloids in the ascites of 3 cases of tuberculous nature gave 195, 196 and 264 mm. pressure. The values were high in the cases of cardiac cirrhosis also. When the colloid osmotic pressure in the ascites fluid is as low as 30 mm. of water this factor is of small importance in the pathogenesis of the ascites and Iversen is of the opinion that the cause in these cases is to be found in the stasis of the liver which produces a considerable increase in the blood pressure in the peritoneal capillaries.

Iversen finds that an ascites fluid which is renewing itself after a puncture contains less protein than the fluid emptied out at the puncture. His idea is that as long as only relatively small areas of capillaries are injured the fluid which is filtered out through these areas and which contains a low concentration of protein is concentrated by reabsorption of water in those capillary areas which are still normal. In this way the fluid may be concentrated until its colloid osmotic pressure is about 200 mm. when further reabsorption is impossible because equilibrium is reached. As larger capillary areas become involved in the stasis reabsorption takes place to a less and less extent and the concentration of protein in

the ascites fluid is decreased A high percentage of protein is thus looked upon as a sign of relatively normal circulation in some areas For such cases where the main cause of the ascites seems to be an increased capillary pressure due to liver stasis Iversen thinks that splenectomy is indicated and has tried thus with success

Among the other diseases with abnormal collections of fluid in the body Iversen together with Hecht Johansen[7] studied a number of patients with fluid in the thoracic cavity due either to cardiac disease or pleuritis

Cardiac Hydrothorax —*In cardiac hydrothorax* these authors find that the transudate contains a rather low percentage of protein but that the percentage is increased if the circulation of the patient is improved through treatment If so a reabsorption of water begins a reabsorption which goes on until equilibrium is attained Hence the better the patient becomes which means the lower his capillary pressure falls—the higher will be the protein content of his hydrothorax fluid

An example showing this is the following A patient with degeneratio myocardii has a hydrothorax the fluid of which possesses a protein content of 1 48 per cent After emptying new fluid is formed which has 1 38 per cent protein and a few days later 1 59 per cent On July 21 and 23 the patient receives salyrgan and on July 25 the protein content is 3 10 per cent Salyrgan is given again on July 26 and the protein increases to 3 45 per cent When no salyrgan is given for four days the protein decreases to 2 83 per cent but rises to 3 65 per cent after a new salyrgan injection There is little doubt that the variations in the protein content of the hydrothorax fluid in a case like this are due to reabsorption of water This reabsorption can go on only until equilibrium is reached which will happen as the protein content approaches 4 per cent (The highest observed value was 4 per cent)

Tuberculous Pleuritis —This value of 4 per cent protein is much less than the concentration often observed in tuberculous pleuritis Here the normal values vary between 3 65 and 6 31 per cent with an average of about 5 per cent This concentration is so high that it is impossible to account for it by reabsorption and the authors maintain that here as in the cases of tuberculous ascites the capillaries are so severely damaged by toxins that they are permeable to most of the proteins of the blood

Edema of Beri beri —Nakazawa has added a disease to the many already known in which we can demonstrate disturbance in the equilibrium of capillary blood pressure and colloid osmotic pressure of the blood as factors at least contributing to the production of edema Together with Seki and Inawashiro[14] he studied the conditions in beri beri In this disease one may find cases either with

or without edema Some stasis is often present The findings on a number of patients showing edema revealed an osmotic pressure lower than that of those with the dry form Many of the patients however had edema with a pressure high above the level at which edema would form if lowering of the protein content were the sole cause a fact easily understood because of the stasis existing in these individuals

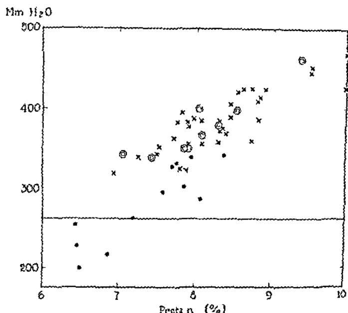


Fig 191 Colloid osmotic pressure and plasma protein in cases of beriberi × Normal cases ○ Dry form ● Edematous form Both normal and pathological values from the material of Nakazawa, Seki and Inawashiro

Summary —We may perhaps sum up the results of the studies by saying that the wide variety of disturbances so far investigated in which extracellular edema is known to exist i e kidney diseases heart diseases ascites hydrothorax anemia and beriberi it has been demonstrated that there is either

1 Decreased colloid osmotic pressure of the blood
2 Increased capillary pressure
3 Injured abnormally permeable capillaries

Or a combination of these factors In these changes we seek the causes of extracellular edema and we are of the opinion that as long as these three factors are normal extracellular edema will not be formed

Effects of Hormones on Edema —There are many questions yet to be settled one of which is What is the mechanism of the undoubted

influence of different hormones on edema? It is well known, for instance, that the institution of insulin treatment is often accompanied by edema formation It is not yet possible to give an explanation of this, but Kylin has observed a considerable decrease in the colloid osmotic pressure of the blood in the cases which developed edema and in some cases he saw the decrease before the edema developed

Tada and Nakazawa[18] have performed experiments which have some bearing upon this question When they inject one of the following four hormones thyroiodin, pituitrin insulin or adrenalin, in rabbits they find that in all cases a decrease in the protein content of the blood results For pituitrin and adrenalin this fall in protein concentration is followed by a decrease in the colloid osmotic pressure of the blood, a decrease which is, however, larger than can be accounted for by the decrease in concentration of the protein

This seems to indicate that these two hormones exert a direct influence on the proteins of the blood so that the specific osmotic pressure of the proteins is reduced and in *in vitro* experiments the authors also find that this happens Both adrenalin and pituitrin depress the colloid osmotic pressure of plasma In spite of this more fluid enters the circulation an occurrence which the author thinks is due to the dominating effect which these hormones have on the capillary pressure If capillary pressure in some areas is depressed because of constriction of the arterioles, the equilibrium between the colloid osmotic pressure and the capillary pressure is disturbed and may result in entrance of fluid from the intercellular spaces into the blood, thus producing a dilution of the blood proteins

References

1 Bing J 1932 Undersøgelser over Albuminuriens Mekanisme (Danish), Bibliot f Laeger, 124, 415–424

2 Epstein 1917 Concerning the causation of edema in chronic parenchymatous nephritis Methods for its alleviation Am J Med Sci, 154 638–647

3 [illegible]

7 Iversen, P, and Hecht-Johansen E 1929 Pathogenese und Resorption von Trans und Exudaten in der Pleura, Klin Wchnschr, 8, 309–310 and Med, 1311–1312

8 Iversen P, and Nakazawa F 1927 Ueber die Biochemie des Filtrationsoedeme, Biochem Ztschr, 191, 307 319

9 Krogh A 1924 The Anatomy and Physiology of the Capillaries, New Haven

[illegible]

73, 328-340

13 Meyer, P 1932 Der kolloidosmotische Druck biologischer Flüssigkeiten. Ergebn d Physiol, 34, 17-111

CHAPTER XXXV

EXPERIMENTAL NEPHROTIC EDEMA *

By LOUIS LEITER M D PH D

CLINICAL NEPHROTIC EDEMA

THE
has be
the as
nepl r
is to the credit of Epstein [1 12] Beckmann[4] and others[13 72] to have analyzed edema fluids from patients with various diseases and laid the foundation for a correlation between the pathogenesis of the edema and the protein content of the transudates Thus experience has been fortified by theoretical deductions in regard to the patho
an experimental attack upon
been made possible because
the edema desired This is
of importance since earlier attempts to produce edema had centered largely upon damage to some excretory organ like the kidney or some transportation system like the vascular or lymphatic network The edema fluid itself was not adequately studied Hence it was not recognized that there might be different kinds of edema fluids depending upon the method of production The quantitative aspect of edema introduced by Epstein rounded out the more or less qualitative picture derived from observation alone and furnished a yardstick by means of which edemas clinical or experimental could be classified Hence we consider the low protein content of

that certain dropsical fluids had a low protein content as revealed by their low specific gravity It is interesting to note that Starling[67] criticized Cohnheim s theory of the inflammatory origin of renal dropsy on the grounds that the low protein content of the edema fluid was evidence against that theory Scattered analyses only such as those of Javal[3] on ascitic fluid are found in the literature Volhard[72] described the transudates in nephrosis as almost a

* From the Lasker Foundation for Medical Research and the Department of Medicine University of Chicago

physiological salt solution"—an apt expression. In 1914 Epstein[11] presented the first systematic analysis of different types of edema fluid, pointed out the very low protein content of certain of these, and a little later[12] correlated these findings with Starling's physiological considerations as to the rôle of the osmotic pressure of the colloids of the plasma in fluid exchange. Beckmann,[4] Fodor and Fischer,[17] Oehme,[66] Falta and Quittner,[13] and Govaerts[20] have published series of determinations establishing the existence of edema fluids with a protein content of about 0.1 per cent or less in the case of subcutaneous anasarca and about 0.5 per cent or less for ascitic fluid. Table 80 presents a summary of their findings.

TABLE 80.—THE LOW PROTEIN CONTENT OF CLINICAL NEPHROTIC EDEMA FLUIDS

Author	Diagnosis	Protein, per cent
Epstein	Nephrotic glomerulonephritis	0.098 to 0.285
Javal[18]	Luetic nephrosis	0.200 to 0.400
Volhard[71]	Nephrosis	0.075 to 0.100
Beckmann	Nephrosis amyloidosis	0.010 to 0.310
Fodor and Fischer[17]	Nephrotic glomerulonephritis	0.030 to 0.140
	Nephrosis	0.070 to 0.150
Hellmuth[ ]	Nephropathy of pregnancy	Less than 0.14 in 19 cases out of 22
Falta and Quittner[ ]	Hunger edema	0.057 to 0.100
Maase and Zondek	Hunger edema	0.116
Jansen	Hunger edema	0.038 to 0.063
Fodor and Fischer	Hunger edema	0.006
Lands and Leopold	Inanition edema, tuberculous enteritis	0.040
Kobayashi[ ]	Beri beri	Less than 0.5 in most, less than 0.? in one-half of cases

Nutritional Edemas as Nephrotic in Type.—During this period of active investigation of clinical edema and related problems, the nutritional privations of the World War reached their climax in the widespread occurrence of the so-called war edema or famine dropsy. This form of anasarca seemed to be independent of demonstrable renal or cardiac disease. It was promptly classified as a "nephrotic" type of edema because it had many clinical features in common with the nephrotic edema of Bright's disease. Most important, the edema fluid had the same low protein content. Hunger edema was obviously a purely nutritional disturbance. Thus it appeared logical to include other nutritional edemas under the same heading. When ever the edema fluids were properly obtained and analyzed, their protein content was found of the same order of magnitude as in nephrosis. The extrarenal nature of the intercellular accumulation of fluid was beyond doubt. One may add to the list of "nephrotic" edemas the anasarcas seen in cachectic states of various origins, in pernicious anemia, in pregnancy, in beri beri, in the complicated nutritional anemias common in India and China, in undernourished

diabetics, in patients with severe diarrheas or short circuited alimentary canal with impaired absorption, and in the nutritional maladjustments occurring during infancy and early childhood. In many of these conditions the edema may be only a minor symptom, in others the entire clinical picture may be dominated by it, and an understanding of the nature of the disturbance in the water balance may lead to more efficient therapy. Table 80 shows that all these edemas have the same low protein content as the dropsical fluid in nephrotic Bright's disease including amyloidosis.

Distribution of Nephrotic Edema.—It has been the custom to

around but shifts to the thighs, lower back and lateral abdominal walls when the recumbent position is assumed. The face is rarely involved. On the other hand, renal edema ordinarily affects the face, especially the loose tissues of the eye-lids, the back of the hands and forearms, the scrotum and labia, in addition to the lower extremities. Renal edema is, therefore, said to be more or less independent of gravity. But, as a matter of fact, even nephrotic edema is to a considerable extent influenced by gravity. In mild cases the edema is usually noticed only in dependent portions, *i. e.*, about the feet or ankles when the patient is up, and about the external genitalia, inner aspect of the thighs and over the sacrum after the patient has been in bed for some time. The rapid dis-

the night, edema accumulates in the relatively low face and it is common to find more swelling on the side of the face that was lowermost

forearms. O

therefore, the

cardiac edema. All types of nephrotic edema, regardless of their origin, tend to predominate in dependent regions of the body and tend to favor areas where the tissues are soft, loose and yielding.

The fluid shifts relatively rapidly with change of position. It is

ties, particularly the peritoneal spaces, are frequently filled with transudate, and there is at times evident an inverse relationship between the amount of ascites and the extent of edema in the lower extremities, depending upon the position of the patient and the corresponding effect on the efficiency of the circulation.

Unlike other forms of edema, nephrotic edema very rarely becomes dangerous to life as a result of involvement of the respiratory tract or the brain Edema of the brain hardly ever occurs In a case reported by Murphy and Warfield[53] it was apparently the immediate cause of death In general, one may say that nephrotic edema is harmful insofar as it impedes locomotion, interferes with the movements of the diaphragm and intercostal muscles, impairs capillary circulation and furnishes a culture medium for pneumococci and streptococci These handicaps to the patient's daily life do not exist when the edema is of moderate extent and there is little fluid in the serous cavities However, the underlying disease, such as nephritis, malnutrition, amyloidosis, etc, may be the source of a number of distressing symptoms unrelated to the presence of edema

Association With Decreased Concentration of Plasma Proteins — Regardless of the disease or condition associated with nephrotic edema, there is always a definite decrease in the concentration of total plasma or serum proteins and usually a striking change in the

extreme decrease in plasma-protein levels and the most marked reversal of the $\frac{\text{albumin}}{\textit{globulin}}$ ratio are found in such conditions as nephritis, nephrosis and amyloidosis, where there is actual excretion of large amounts of formed proteins The few carefully studied cases — to fall undi- retion

of the plasma proteins and prevents their proper replenishment In the various types of nutritional edemas, including those seen in the anemias and in cachectic and malignant states all degrees of reduction in the concentration of the plasma proteins may be found The data in Table 81 illustrate this point No attempt

analysis In general, it is rare to find any considerable degree o nephrotic edema when the total plasma protein concentration chemically determined, is above 5 per cent and the albumin fraction above 2 per cent At any rate the response of edema to therapeutic

measures is more prompt and permanent at or above these levels for total protein and albumin than below When the plasma proteins are markedly reduced and albuminuria persists unchecked, the edema is likely to be a stubborn manifestation not yielding to diuretic measures Fortunately such cases of extensive anasarca are rare nowadays owing to the more intelligent recognition and treatment of the early stages The formation of large quantities of a transudate may itself appreciably deplete the plasma proteins to a critical level in spite of the low percentage of protein in the fluid The repeated removal of ascitic fluid by paracentesis may be as severe a drain upon the plasma proteins as a moderately severe albuminuria

TABLE 81 —THE PROTEIN CONCENTRATION OF THE SERUM OR PLASMA IN CLINICAL NUTRITIONAL EDEMAS

Author	Diagnosis	Plasma protein per cent
Schittenhelm[83]	Hunger edema	3 94 to 7 0 in 41 cases of 48 (R)*
Jansen[30]	Hunger edema	4 0 to 6 4 in 30 cases of 40 (R)
Wolferth[3]	Inanition edema	3 30 to 4 60 (R)
Mozai *et al*[2]	Beri beri	Less than 7 0 (R)
Peters *et al*[54]	Advanced pulmonary tuberculosis	3 68 to 5 63
	Intestinal tuberculosis emaciation	3 44
	Jejunocolic fistula	3 69
Meulengracht *et al*	Pernicious anemia	5 0 to 7 31 (R)
Palmer[5] †	Gastro-jejunocolic fistula	71 to 4 27
Landis and Leopold[8]	Tuberculous enteritis	3 6 (R)

HISTORICAL REVIEW OF EXPERIMENTAL EDEMAS

Older Theories of Renal Edema and Their Influence Upon Experimental Work —Bearing in mind the above discussion of clinical nephrotic edema the shortcomings of the earlier experimental work become manifest since no clear division was drawn between the different kinds of so called renal edema and little effort was expended to determine the quantitative nature of the edema fluid with the exception of the chloride content To a large degree, the experimental attack upon edema followed the theoretical concepts laid down by the great clinicians of the nineteenth century who interested themselves in the problems of Bright s disease It may be appropriate to sketch briefly their theories of renal edema and to show how certain experimental edemas were bound up with these ideas The fruitfulness of these viewpoints of busy, but physiologically minded clinicians to the investigators in contact with them is well illustrated in this field of medical research

* (R) indicates refractometric analysis Chemical methods were used by the other authors

† Unpublished data of Dr W L Palmer Department of Medicine University of Chicago

Bright,[7] dealing largely with the subacute and chronic forms of renal disease, was struck by the quantitative significance of the proteinuria and was probably not surprised to find the decrease in plasma proteins. He assumed that the thin, watery or "hydremic" condition of the blood plasma made it more easily filtrable into the tissue spaces. Curiously enough, the reverse of this process, the return of fluid from the tissue spaces into the blood, was apparently not related to the altered composition of the blood. Thus Bright missed the opportunity that Starling grasped in a flash of genius some sixty years later. Bright's concept of hydremia as due to a decrease in plasma proteins was, however, correct, although almost a hundred years elapsed before direct proof was brought foward in the work on plasma-volume and plasma-protein concentration by the Van Slyke group.[45,46]

Stewart[83] and Bartels[3] were more impressed by the oliguria associated with periods of nephritic edema and assumed the former to be the cause of the latter by way of "hydremic plethora" or a true increase in plasma volume.

Senator,[80] while recognizing the inadequacy of Bright's theory for the edema of acute nephritis in which dropsy often occurs early in the disease before much plasma protein can have been lost with the urine, realized equally well that Bartels' reasoning as to the importance of oliguria was less applicable when the chronic forms of renal edema were considered. But like his predecessors he searched for an all-embracing concept to explain all forms of renal edema on a uniform basis. He extended the idea of capillary damage in renal disease to apply to the cutaneous, peritoneal and other capillaries instead of to the glomerular capillaries alone. In this way, increased capillary permeability readily explained the edema of acute glomerulonephritis and could be stretched to cover chronic renal edemas as well, although Senator admitted that "hydremia" (low plasma protein level) was also a factor in the anasarca of amyloidosis and other conditions associated with wasting.

These theories of Bright, Bartels and Senator are all partially correct—Bright's theory, when applied to chronic nephrotic edema, Bartels' theory, when considering the edema of acute oliguria and anuria of non-inflammatory origin (*e. g.*, mechanical obstruction of the urinary tract, mercurial poisoning, etc.) and the true renal retention of water in terminal uremic states, Senator's theory, when used to explain the early edema of acute glomerulonephritis. These three factors—*hydremia, insufficient excretion of water* and *capillary damage* are as important today as fifty years ago.

Experimental Edema as the Result of Vascular Damage and Increased Capillary Permeability.—The experimental study of edema proceeded *pari passu* with the development of the above theories with the exception of the view of Richard Bright, which was not

adequately investigated Most of these experiments have become classical and need little description Bartels' theory of hydremic plethora as the cause of renal edema was put to the experimental test by Cohnheim and Lichtheim,[9] Magnus[49] and others In experiments involving the intravenous injection of enormous quantities of fluid, the rôle of hydremic plethora or increased plasma volume, was found to be a subsidiary one in the production of edema while vascular damage, brought about by various chemical or physical irritants, was shown to be of prime importance In short, Senator's idea concerning the increased permeability of damaged capillaries was confirmed and the analogy was drawn with the changes in the cutaneous capillaries in scarlet fever In none of these studies was the edema fluid analyzed for protein but the nature of the procedures seem to leave little doubt but that the fluid was a protein-rich exudate and therefore entirely unrelated to nephrotic edema

A **The Non-nephrotic Edemas** —1 **Uranium Edema** —Senator's views found further experimental support in the work done on the toxic nephropathies especially uranium poisoning Richter[60] showed that under certain conditions uranium nitrate could produce edema in association with renal damage whereas other poisons [illegible]

[illegible]

demonstration of what many had suspected ever since the work of Cohnheim and Lichtheim namely that renal damage was one factor only and at times a relatively unimportant one in the production of so-called renal edema, while general capillary injury was of primary significance Of course the oliguria the extent of extrarenal loss of fluids and the supply of water and salts were found to be important accessories in the production of edema by uranium nitrate These factors however were of importance in all types of edema It should be noted that the most successful results were obtained in the rabbit—an animal which does not perspire and cannot vomit and, therefore is at a serious disadvantage when its kidneys are excluded from function and something like 50 cc of water per kg of body weight are given to the animal It would seem that Bartels theory of renal retention of water would apply to these experiments just as it undoubtedly does in nephrectomized animals

High Protein Content of Uranium Edema Fluid —In connection with uranium edema one finds the first systematic analyses on the protein content of the edema fluid usually ascitic Georgopulos[16] [illegible]

fibrinogen content and point to considerable injury of the capillary endothelium In the last few years more data on uranium edema have become available through the repetition of this work by French and Belgian investigators Thus Garnier Schulmann and Marek,[19] Nau[54] Schulmann and Marek[64] and Govaerts[23] have reported the protein content of ascitic fluid as between 1 and 4 per cent (Table 82) Obviously one is dealing with an exudate resembling the fluid in a blister more closely than ordinary nephrotic edema fluid

TABLE 82 —THE HIGH PROTEIN CONTENT OF SOME EXPERIMENTAL EDEMA FLUIDS

Author	Method	Protein per cent
Georgopulos[29]	Uranium nitrate	0 34 to 3 85
Garnier *et al* [19]	Uranium nitrate	2 60
Schulmann and Marek[64]	Uranium nitrat	2 30
Nau[54]	Uranium nitrate	2 80 to 5 1 (*total sol ds*)
Govaerts[23]	Uranium nitrate	1 90 to 2 80
Tainter and Hanzlik	Paraphenylenediamine	Very high (*whole plasma*)
Bolton[5]	Partial venous obstruction	6 50 to 7 90 (*total sol ds*)
Farmer *et al*	Nephrectomy	1 26 to 3 01

2 **Paraphenylenediamine and Mustard Oil Edema** —The physical characteristics and the high protein content of uranium edema fluid allow an easy transition to the frankly inflammatory edemas local and more or less general produced by such poisons as paraphenylenediamine and mustard oil This group of edemas is interesting for three reasons (1) Because the kidneys are not implicated (2) because direct vascular damage has been shown to be the mechanism involved (3) because this group lends itself to rigidly controlled experiments The work of Hirschfelder[29] Hunter and Hanzlik[7] and Tainter[70] is characterized by strict adherence to the scientific method of controlling one factor after another These investigators have demonstrated that local capillary injury is the direct cause of exudation while the amount of edema depends upon the mechanical factors of the circulation such as capillary pressure and blood flow In other words the theories of Ludwig Cohnheim and Starling have been confirmed The edema produced in these experiments indicates a marked increase in vascular permeability the whole plasma passing out of the capillaries to clot in the tissue spaces Nephrotic edema represents the other extreme inasmuch as no change in capillary permeability to protein is demonstrable except in the glomeruli when there is albuminuria Nephritic cardiac and other non nephrotic edemas fall between these two extremes

3 **Experimental Edema by Mechanical Obstruction in the Circulatory or Urinary System or as the Result of Nephrectomy** —Several groups of experiments may be mentioned representing a combination of renal mechanical and permeability factors in varying degree Bolton[5] using a method for partial occlusion of the inferior vena

cava above the diaphragm was able to produce in cats a small amount of ascites that persisted or reformed for a few months until collateral circulation was established This essentially cardiac ascites was rich in solids chiefly protein The change in permeability here is easy to understand while increased capillary filtration pressure undoubtedly aggravates the situation Lyon Shafton and Ivy[47] and Farmer Barry Reed and Ivy[14] have produced edema in nephrectomized dogs by the subcutaneous administration of Ringer s solution The injected fluid is evidently absorbed redistributed by the circulation and deposited in the serous cavities and subcutaneous tissues as true edema This edema is analogous to the terminal retention of water in patients with contracted kidneys or with complete obstruction of the urinary tract It may also have some bearing upon the edema developing in acute renal disease with oliguria or anuria In all of these conditions the same situation must prevail as in the rabbit poisoned by uranium that is fluids must be forced beyond the animal s capacity to dispose of it in the presence of non functioning kidneys The reason why edema is not more often seen in terminal uremic states with oliguria is probably that the patients are losing more fluids by way of the gastro intestinal tract than they are receiving orally or parenterally That renal retention of water can play an important role when other sources of elimination are lacking and the intake of fluids is is not reduced has been shown by McClure[43] Swingle[69] Adolph[1] and Brugsch Cahen Horsters and Rothmann[8] These investigators produced marked edema in frogs or tadpoles by tying off the cloaca or both ureters or extirpating the kidneys after which the animals were kept in water Since the osmotic absorption of water by the frog s skin goes on continually regardless of the requirements of the animal or the capacity of the excretory system to handle the fluid, edema is easily obtained A better illustration of renal retention of water is difficult to find Whether in any of these experimental edemas there are significant changes in the volume or composition of the plasma cannot be determined from the published reports

In regard to the protein content of the edema fluid no data are available on the frogs but Farmer Barry Reed and Ivy[4] have found well over 2 per cent of protein in the ascitic fluid of their nephrectomized dogs indicating a considerable increase in permeability of the capillaries due to unknown toxic agents This type of edema associated with true uremia is not nephrotic in character and should not be correlated with clinical nephrotic edema

B The Nephrotic Edemas 1 Experimental Nutritional Nephrotic Edema in Rats Up to this point none of the experimental edemas discussed has borne out the fundamental features of nephrotic edema

A fairly close relationship could be shown between some of these and acute nephritic edema in man the elements of vascular injury and the high protein content of the edema fluid being common to all of them It was not until the epidemic of war edema began to be understood that attempts to reproduce nutritional edema in experimental animals were carried out Denton and Kohman[10] and Kohman[38] obtained dropsy in rats which had been kept for several weeks on a low protein (carrot) diet otherwise adequate for nutrition and growth Increase of protein in the diet lead to disappearance of the edema The fluid intake was found to be an important factor The edema did not appear until definite emaciation had developed This observation pointed to an exhaustion of body protein The significance of this nutritional edema lay in the fact that no toxic agent was involved that might alter capillary permeability Here a nephrotic edema had apparently been obtained Mayer[50] obtained similar results Some years later Frisch [illegible]

2 **Nephrotic Edema in Monkeys** The edema developing in a long dietary experiment on a monkey reported by Harden and Zilva[24] probably falls into the same group Emaciation was an evident factor The author has observed instances of spontaneous anasarca in laboratory monkeys One monkey* had a definite nephrotic edema with typical low serum proteins and very little protein in the edema fluid The edema involved dependent portions but was also noticeable on the face in the early part of the morning It gradually disappeared on a generous mixed diet Autopsy later on disclosed neither cardiac nor renal pathology This as far as is known represents the first established instance of nephrotic edema in the monkey The primary cause of the condition could not be established Diarrhea occurred intermittently during the period of edema A detailed study will be published elsewhere

3 **Experimental Nutritional Edema in Man** —The availability of markedly undernourished individuals in Central Europe during the World War made possible interesting experiments on edema Thus Falta and Quittner[13] brought on a nephrotic type of edema in emaciated diabetics and non diabetics by forcing fluids and salt along with large amounts of sodium bicarbonate This regime is not effective in individuals with a normal state of nutrition Jansen[31]

* It was through the kindness of Dr I S Falk formerly in the Department of Hygiene and Bacteriology of the University of Chicago that this opportunity was afforded as the monkeys belonged in his experimental stock and he made the original observations

obtained similar results on an emaciated woman with a malignant esophageal stenosis and a gastric fistula The low protein content of the plasma in this type of edema is shown in Table 81

4 **Experimental Bromide Edema in Dogs** —The edema produced in dogs by the combined administration of sodium chloride and sodium bromide, as reported by Hastings and Van Dyke,[26] represents an [illegible]

kidneys The edema fluid has a low protein content [25]

PLASMAPHERESIS

The problem that presented itself in 1925 was the direct production of experimental nephrotic edema without damage to the kidneys or injury to the capillary [illegible]
the forces involved in [illegible]
tissue spaces Since th[illegible]
ling's[66] classical work on the osmotic pressure of the plasma proteins, evidence had accumulated to prove the connection between albuminuria, low plasma proteins decreased colloid osmotic pressure of the plasma and the development of nephrotic edema This sequence was virtually a return to Richard Bright's brilliant guess with the addition of a mechanism for drawing tissue fluids back into the blood Supported by the determinations of the osmotic pressure of the plasma proteins by the Krogh school,[37] by Govaerts [21] Schade and Claussen,[62] Rusznyák[61] and others the *Starling-Epstein-Krogh* theory of nephrotic edema, as we may call it, was an enormous advance over the theories of tissue or colloid affinity for water, or of 'increased permeability' to water and salts in only one direction through the capillary It seemed desirable to attempt to forge the last link in this chain of evidence, that is the production of edema by a rapid and continual loss of plasma protein in an experimental animal If obtainable, the edema fluid should in accordance with the theory, have a low protein content This was the crux of the problem and needs emphasis because investigators have overlooked this point to the extent of not determining the protein content of the edema fluid It was at the suggestion and with the encouraging guidance of Dr D D Van Slyke that work on this problem was begun at the Hospital of the Rockefeller Institute in 1925 The experiments were continued in the Department of Medicine of the University of Chicago from 1927 on, thanks to the generous support and faithful interest of Dr Franklin C McLean

The Method —**Plasmapheresis as a Substitute for Albuminuria** —The method employed consisted essentially in the direct removal of the plasma proteins in dogs by the process of plasma depletion

so successfully employed by the Whipple school[33 34 35] The dogs were bled from the heart or jugular veins instead of the accessible arteries The details have been described by Leiter[33] By this method a rather crude imitation of chronic albuminuria was achieved, with the advantage of avoiding any direct damage to the kidneys The animals were on the usual stock diet unrestricted as to water and given daily about 1500 cc of 0 85 per cent sodium chloride solution by stomach tube to ensure an adequate supply of the elements of edema fluid Analyses of the blood and the transudates were carried out by means of standard chemical procedures Material from organs or tissues at autopsy was worked up in the usual histological manner



Fig 1 Dog 11 in recumbent position to show the edematous abdominal wall and the swelling of the thighs

The Results Low Plasma Proteins and Edema in Dogs — Adequate plasma depletion requiring the daily bleeding of 10 kg dogs to the extent of 800 to 1000 cc promptly leads to a progressive fall in the concentration of the plasma proteins so that usually within three or four days values of about 3 per cent are obtained representing about one-half of the normal concentration in dogs At this point if plasma depletion is still continued in order to offset the rapid regeneration of the plasma proteins edema makes its appearance and increases progressively This is shown simultaneously in the rising weight curve gains of 10 to 30 per cent often occurring within a few days to be followed by equally striking drops in weight when edema disappears The extent of edema depends on many factors but chiefly upon the possibility of maintaining the plasma protein level below the critical concentration This varies with the individual dog However no exception has been found to the rule that edema always appears in the dog whenever the plasma

proteins have been reduced to about 50 per cent of their normal value and kept at or below this level. Should plasma depletion be discontinued for one or two days a sufficient rise in the plasma protein concentration occurs to bring it above the edema level and the process shifts in the direction of rapid diuresis and complete disappearance of edema. This reversible reaction has been observed with great regularity. The change from a state of edema to one of no edema occurs so rapidly with the elimination of only one factor, plasma depletion, that a cause and effect relationship between reduced plasma proteins and impaired reabsorption of fluid from the tissue spaces can scarcely be questioned. Edema has been produced in varying degrees in about 40 dogs. Figs. 124, 125 and 126 illustrate the sequence of events in these experiments.

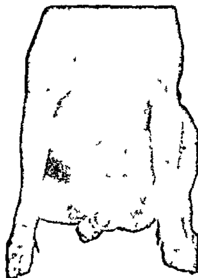


Fig. 123.—Marked edema of the abdominal wall and external genitalia, also ascites in Dog 11.

Distribution of Edema.—The edema is first noticeable in the soft tissues about the inner aspect of the thighs, the external genitalia and the inguinal region. It pits readily and can easily be squeezed from one subcutaneous area to another. As the edema increases, the buttocks and perineal region become more swollen, the posterior aspect of the thighs down to the knees is involved and the hind legs become rounded out. The abdominal wall becomes definitely edematous, at first in the suprapubic and lower lateral regions, later all the way up to the costal margin. In extreme cases the anterior

Fig 124 —Dog 11

Fig 125 —Dog 16

and lateral chest walls are also involved and occasionally the neck develops rolls of edematous tissue The forelimbs are usually unaffected Ascites usually makes its appearance early may increase to 1000 cc or more and be associated with respiratory embarrassment Hydrothorax and pulmonary edema have been observed in extreme instances and have at times been the immediate cause of death

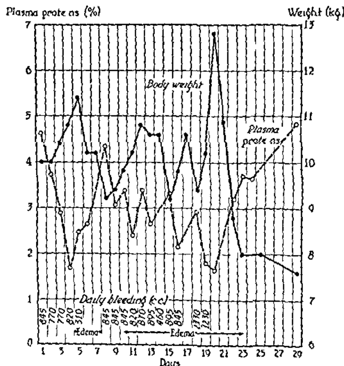


Fig 126 —Dog 17

The subcutaneous edema fluid is always freely movable in the tissue spaces and responds readily to changes in the position of the animal When the dog is tied down on his back the swelling rapidl
geni
the p
inclu
for s
inal
port ... external genitalia but

Distribution of the excess fluid in the tissues is closely analogous to that seen in human anasarca The loose areolar layers in the subcutaneous tissues are filled out with a clear or slightly opalescent fluid which also extends into the intermuscular planes and into the connective tissue septa between the muscle bundles The greatest amount of fluid is found between the upper dermis and the muscular level The properitoneal and retroperitoneal tissues are infiltrated

€

section of edematous abdominal wall illustrating the typical separation of collagen bundles by the accumulation of a large amount of intercellular fluid

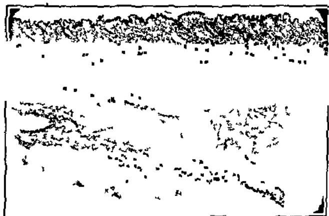


FIG 127 Typical edema of the skin and subcutaneous tissues of the anterior abdominal wall of Dog 10 Low magnification

There is little question as to the free nature of the edema fluid even early in its development Needle punctures or other injuries to the skin overlying an edematous area lead to constant oozing or

simple matter When obtained without any admixture with blood the subcutaneous fluid is colorless water clear or slightly opalescent Ascitic fluid is more likely to be opalescent

Low Protein Content of the Experimental Transudates —The composition of this experimental transudate is of the greatest significance insofar as it concerns the protein content In regard

the significance of Starling's insistence upon the distinction between the fluid in the potential tissue spaces and lymph as collected from some duct True tissue fluid cannot be obtained for analysis, but the striking difference in the protein content of lymph from different regions of the body indicates that there is a difference in the permeability of the capillaries for the plasma proteins Since the peripheral capillaries in contrast to those of the abdominal viscera are the most impermeable to protein under normal conditions, edema fluid formed in the periphery should have a very low, or negligible protein content provided that no injury of the capillary endothelium exists to alter the normal impermeability The high protein content of most of the experimental edemas reviewed earlier in this chapter is due to direct damage of the capillary walls by what are known as vascular poisons These edemas might be considered as exudates rather than transudates Nephrotic edema is simply an ultrafiltrate of the plasma theoretically dependent on a disturbance in the equilibrium of the physical forces controlling the water balance between the blood and tissue spaces and independent of hypothetical changes in the permeability of the capillaries to salt and water since the latter pass freely in both directions at all times The criterion for the nephrotic nature of an experimental edema is the low concentration of protein in the edema fluid

FIG 53 —THE LOW PROTEIN CONTENT OF EXPERIMENTAL NEPHROTIC EDEMA IN DOGS (LEITER [illegible])

Dog No	Edema fluid	Protein per cent
10	Ascitic	0 04
	Ascitic	0 12*
	Ascitic	0 0[illegible]
11	Ascitic	0 47
	Ascitic	0 [illegible]4
	Subcutaneous	0 [illegible]
14	Ascitic	0 4[illegible]
15	Ascitic	0 35
	Ascitic	0 0[illegible]
	Subcutaneous	0 0[illegible]
16	Ascitic	0 39*
	Ascitic	0 11*
17	Subcutaneous	0 0[illegible]*
	Subcutaneous	0 0[illegible]*
2[illegible]	Subcutaneous	0 0[illegible]
	Ascitic	0 75
3[illegible]	Ascitic	0 04
	Subcutaneous	0 01
33	Ascitic	0 04
[illegible]	Ascitic	0 34
	Subcutaneous	0 04
37	Ascitic	0 0[illegible]
41	Ascitic	0 09
	Ascitic	0 12
50	Ascitic	0 01*
	Ascitic	0 10*

* Only the total nitrogen was estimated on the edema fluid The plasma non protein nitrogen value was used in calculating the protein content

The chemical analyses of subcutaneous and ascitic transudates have given gratifying results Table 83 shows the figures for the earlier experiments All but one of the values for the protein content of subcutaneous edema fluid fall below 0 1 per cent while those for ascitic fluid are usually below 0 3 per cent It is interesting that many values fall within the range for the protein content of cerebrospinal fluid considered by many investigators as an ultrafiltrate of the plasma These figures compare favorably with those shown in Table 80 for clinical nephrotic edema It seems that these analyses establish for the first time the production of nephrotic edema in an experimental animal

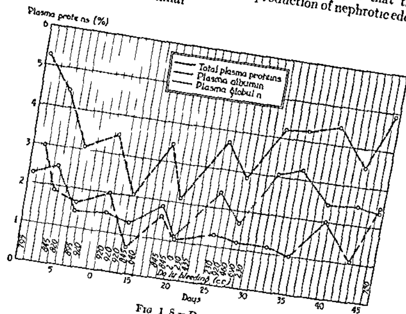


Fig 1 8 —Dog 90

Regeneration of Plasma Albumin and Globulin During Plasma Depletion —During the course of these experiments one could not help being struck by the capacity of the dogs to regenerate their plasma proteins Kerr Hurwitz and Whipple[33 34 35] have worked out very thoroughly the conditions for regeneration following acute depletion of plasma proteins in dogs but their method of plasmapheresis did not give them the opportunity of carrying on chronic experiments The persistent reversal of the albumin

plasma of not

known

globulin

fractions during periods of ... able to follow the course of these ... albumin and ... periods of prolonged plasmapheresis interspersed

with periods of remission The results are illustrated in Fig 128 It is obvious that while at first the curves for total protein albumin and globulin parallel each other later there is a sharp separation so that with each respite from plasma depletion the total protein and globulin curves rise sharply but the albumin curve lags behind and tends to remain flat over long periods It seems as if the regeneration of plasma globulin is a rapid process while albumin is more slowly formed Hence the $\frac{\text{albumin}}{\text{globulin}}$ ratio remains low for some time The tendency to edema is determined not by any specific albumin or globulin level but rather by such a combination of the two that the total plasma protein osmotic pressure is less than the value necessary to prevent an excess of filtration over reabsorption of fluid in the capillaries

When plasma depletion has continued for weeks or months the animal is likely to become emaciated even in the absence of infection

served of failure to increase the plasma globulin as soon as depletion was temporarily discontinued regardless of the state of nutrition of the animal Considerable time may be required however for complete restoration to the normal level

Changes in Blood Cholesterol During Plasmapheresis —The blood cholesterol was followed in many experiments in order to determine whether there was any analogy with the condition occurring in nephrotic glomerulonephritis and nephrosis Some investigators believe that the high blood-cholesterol level in active nephrotic renal disease is somehow related or secondary to the decrease in the plasma proteins [16] Others think that it represents a primary disturbance All admit that the blood cholesterol is characteristically and persistently elevated in nephrotic renal disease Recently Barker and Kirk[3] stated that the blood cholesterol in dogs undergoing plasmapheresis becomes elevated thereby producing a picture

associated with prolonged undernutrition or inanition in man and tends to rise only with improved nutrition

The results fall into two main groups as reported previously [40] First there are the experiments of short duration say less than two weeks in which plasma depletion is associated with either a fall or at times a considerable rise in blood cholesterol unpredictable and

varying from dog to dog In the second place come the longer experiments in which, after the first irregularities the blood-cholesterol curve seems to follow a rather definite cycle, tending to [illegible]

as plasma depletion begins anew

Any attempt to explain the blood-cholesterol curves in the dogs at present is purely speculative, since little is known as yet about fat metabolism under varying conditions The situation in nephrosis in man has been reviewed by Leiter,[12] who pointed out some of the more obvious defects in the knowledge of this problem If one may speculate, it would seem that the marked fluctuations occurring in the blood cholesterol during short depletion experiments may represent a resultant of such factors as the washing out of plasma cholesterol, the mobilization of cholesterol with the fats from the fat depots and its transport in the circulation, and alimentary hyper cholesterolemia, to mention only the more important ones On the other hand, in the long experiments each period of plasma depletion is associated with a considerable loss of blood cholesterol while, in the *interim* between bleedings, the supply of endogenous and exogenous cholesterol to the blood is perhaps not as rapidly taken care of by the liver of the undernourished animal as normally Hence the blood cholesterol rises sharply and remains elevated until equilibrium between supply, transport and removal is reestablished This is only a working hypothesis and requires confirmation by further experiments The hypercholesterolemia produced in rabbits by frequent bleeding as reported by Fishberg and Fishberg [16] is apparently a process quite different from the situation in the dogs during plasmapheresis

THE RELATION BETWEEN THE EXPERIMENTAL AND CLINICAL NEPHROTIC EDEMAS

The Experimental Edema as a Pure Nephrotic Type —From the review of the clinical nephrotic edemas and the consideration of the previous forms of experimental edema it seems fair to conclude that the edema just described may be classified as a nephrotic type It represents a rather pure form of nephrotic edema in comparison to that seen in nephrotic glomerulonephritis, because in the latter there occur transitions between nephritic and nephrotic edemas making interpretation at *times difficult* The experimental dropsy in the dog has been shown not to be cardiac in origin[44] and is unrelated to renal function or pathology, although the kidney may show various lesions directly or indirectly connected with the

experimental procedures used Vascular damage is ruled out by the composition of the edema fluid In short the factors assumed to be responsible for the experimental edemas previously described with the exception of the nutritional edemas in rats are here absent or unimportant The theory of Starling as elaborated by Epstein

at first glance so unrelated to one another

Experimental Nephrotic Edema in Dogs is not Nephrosis —It seems probable that all that has been produced is a disturbance in

than edema to make any one of these states although edema may be the outstanding feature To produce real experimental nephrosis there must be present the characteristic disturbances in lipoid metabolism the cholesterol-ester infiltration of the renal tubular epithelium the doubly refractile lipoid droplets in the urine to mention only the most obvious findings in clinical nephrosis Such a picture has never been produced The author has examined many

except occasionally at the borders of and in organizing infarcts The blood-cholesterol curves have already been described and the lack of resemblance to human nephrosis seems clear It must be agreed upon that the experimental edema in dogs is nephrotic but not nephrosis

The Time Factor in Nephrotic Edemas —The edema in dogs is produced too rapidly a matter of a few days to be entirely analogous with the nutritional edemas of man and those observed in rats and other animals The factor of time however must not be forgotten Where undernutrition is a gradual process there is ample time for readjustment and the human body can carry out a conservation p
tration in
level for a
or protein builders in diarrheal stools In patients with active nephrotic renal disease the continual albuminuria is the serious occurrence Yet the human body can regenerate plasma proteins fairly well since a nephrotic patient may maintain a constant plasma protein level for months in spite of the loss of 10 gm of protein per day A 10-kg dog often does better than that In the dog experiments there is little time for adaptation the physical

mechanism for maintaining the water balance is taken by surprise and edema can be produced long before any emaciation has occurred. This seems to indicate that emaciation *per se* is not a *sine qua non* for nutritional edema. The prompt response to proper therapeutic measures in the clinical cases indicates the subsidiary rôle of loss of body weight.

THERAPEUTIC PROBLEMS AND PRINCIPLES

Problems of Therapy in the Nephrotic Edema of Man and Dog. — Clinical nephrotic edema is a chronic process when found in association with renal disease because the fact that albuminuria has persisted long enough to reduce significantly the plasma protein level makes a sudden cessation or decrease in albuminuria unlikely. In these patients restriction of salt and fluid in the diet may have little effect upon an existing edema if at all extensive. The problem then is how to stimulate more rapid formation of plasma proteins in order to overbalance the loss in the urine.

The dog with experimental nephrotic edema at first is unable to restore plasma protein as rapidly as it is being removed but within a few days the supply almost equals the demand. When plasmapheresis then is discontinued for only twenty-four or forty-eight hours the stimulus to regenerate the proteins is effective enough to raise their concentration in the plasma above the edema level. Marked diuresis sets in and edema disappears rapidly, in spite of the continued administration of large amounts of isotonic salt solution by stomach tube. In the dog, therefore, we are dealing with an acute, easily reversible nephrotic edema that requires no treatment other than to check the drain upon the plasma proteins.

The non-albuminuric nutritional nephrotic edemas observed clinically form a sort of combination of chronic and acute insults, the chronic damage being represented by a long period of gradual emaciation and a slow fall in the plasma proteins, the acute being manifested often in a temporary severe diarrhea or some infection followed by a period of relatively huge intake of salted fluids, such as soups, to appease the urge for food. The edema appears shortly thereafter and may or may not spread rapidly. The relatively simple procedure of rest in bed and restriction of salt and water may be highly effective in bringing about the disappearance of edema provided the plasma proteins are not too low. When these are very much reduced, edema may not decrease in spite of the limitation of water and salt. Just how low this protein level must be is not known at present. It is in this non-albuminuric group that blood or plasma transfusion would seem to be the most hopeful measure for rapidly raising the plasma proteins above the critical

edema level A successful instance of this therapy was recently reported by Landis and Leopold[38]

Principles of Therapy in Nephrotic Bright s Disease —The principles of therapy in what are to clinicians the most important and the most difficult cases of nephrotic edema that is in nephrotic Bright s disease may be derived from further consideration of the relation between experimental nephrotic edema and the clinical forms In both animals and man the capacity for regeneration of the plasma proteins is almost unlimited The human being however sooner or later acquires a distaste for food for diverse reasons or acquires what is worse wrong suggestions and advice concerning

h less

what

letion

rate

Until recently patients with nephrotic Bright s disease were treated

better to make certain first of an optimal rather than a minimal protein intake second of an appetizing variety of foods to make possible a high caloric diet necessary to overcome the existing undernutrition masked by the edema and third of a limitation of salt and fluids insofar as it is consistent with the adequate consumption of food Furthermore with protein continually being lost in the urine it would seem inadvisable to remove by paracentesis collections of even a low protein ascitic or other transudate The total amount of plasma protein discarded in this manner becomes quite significant Conservatism is therefore indicated unless the patient s condition warrants rapid action The nephrotic patient is ordinarily not treated sufficiently while his edema is given too much treatment In a condition that takes considerable time to develop sufficient time must be allowed for dietary or other measures to work Under conditions not understood at present even the albuminuria may diminish to a point where it is no longer a serious loss of protein The plasma proteins then increase above the edema level although the rate of this process in relation to the degree of albuminuria is practically unknown Edema disappears and the patient may be in apparently good health for a

another they have been stressed repeatedly in the last thirty years They still need repetition in view of the prevailing confusion in the practice of the healing art in this branch of medicine

ADDENDUM

Since this chapter was written considerable evidence has accumulated in the literature confirmatory of the basic conceptions of nephrotic edema. In regard to clinical nephrotic edema the predominating role of undernutrition or loss of plasma protein from the body by various routes has been firmly established by the studies of many investigators[74, 8, 86, 88, 89, 9]. The importance of their findings in stimulating rational dietary therapy cannot be overemphasized.

Experimental nutritional nephrotic edema has been produced in the dog by Shelburne and Egloff[90] using a diet low in protein but adequate in other respects. There was a close analogy between this nutritional edema and plasmapheretic edema. Weech, Snelling and Goettsch[9] have made a more extensive study with these two methods of producing nephrotic edema in dogs and have stressed the significance of the plasma albumin level in relation to the appearance of edema. The low protein content of experimental nephrotic edema fluid was confirmed by these investigators. Bloomfield[75, 76] has reopened the problem of carrot edema in the rat by failing to produce low serum proteins or edema in mature rats on low protein diets not containing carrots.

Plasmapheretic edema in dogs has been reproduced by many investigators. Darrow, Hopper and Cary[77, 78] made careful studies of the electrolyte pattern of the serum and ascitic fluids in their edematous dogs. Lepore[84] investigated the distribution of chloride and water in various tissues and organs. Fahr and his associates[79] emphasized the salt factor in experimental edema. Kumpf[83] bled

The quantitative relationships between venous pressure ... osmotic pressure of the blood and rate of filtration of fluid through the capillary wall in normal human subjects have been determined by Krogh, Landis and Turner[8]. Their results are in full accord with the Starling-Krogh-Epstein theory of nephrotic edema as a quantitative disturbance in the normal mechanism of fluid balance. Loeb and his associates[87] arrived at a similar conclusion after a ... normal individual and ...

Cl and NaCl

... in the regeneration of plasma protein has recently been attacked ... an ingenious manner by Holman, Mahoney and Whipple[80, 81] who have calculated the amount of new plasma protein formed in the dog under standard conditions in response to various dietary proteins. Further development of this line of investigation may have far reaching effects upon the treatment of clinical nephrotic edema.

REFERENCES

1 ADOLPH, E F 1927 The excretion of water by the kidneys of the frog, Am J Physiol, 81 315–324

2 BARKER, M H, AND KIRK, E J 1930 Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients, Arch Int Med, 45, 319–346

3 BARTELS, C 1875 Handbuch der speziellen Pathologie und Therapie, Leipzig vol 9

4 BECKMANN, K 1921 Oedemstudien II Untersuchungen über den Eiweissgehalt und intermediären Zucker, Wasser- Harnsäure und Kochsaltzwechsel bei verschiedenen Oedemformen Deutsch Arch f klin Med, 135, 39–67

5 BOLTON, C 1910 An experimental study of the pathology of cardiac dropsy and its relation to that of local venous obstruction J Path and Bact 14, 49–89

6 ———— 1921 Absorption from the peritoneal cavity J Path and Bact, 24 429–445

7

8

Oedem

9

isches

10

and bc

11 EPSTEIN A A 1914 Studies on the chemistry of serous effusions, J Exp Med, 20, 334–315

12 ———— 1917 Concerning the causation of edema in chronic parenchymatous nephritis method for its alleviation Am J Med Sci 154 638–647

13 FALTA W AND QUITTNER M 1917 Ueber den Chemismus verschiedener Oedemformen Wien klin Med 30 1189–1196

14 FARMER C J BARRY I S REED A AND IVY A C 1930 Experi-

...s by low protein diets

I 1928 Toxicité du Compt rend Soc de

20 GEORGOPULOS 1906 Experimentelle Beiträge zur Frage der Nierenwassersucht Ztschr f klin Med 60 411–471

27 Heineke, A, and Meyerstein, W 1907 Experimentelle Untersuchungen über den Hydrops bei Nierenkrankheiten, Deutsch Arch f klin Med, 90, 101-131
28 Hellmuth, K 1922 Refraktometrische Eiweissbestimmungen der

Med, 131, 330-310
32 Javal, A 1910 Lactescence du sérum et du liquid d ascite dans un

Haven
38 Landis, E M, and Leopold, S S 1930 Inanition edema associated with tuberculous enteritis, J Am Med Assn, 94, 1378-1381
39 Leiter, L 1928 Experimental edema, Proc Soc Exp Biol Med, 26, 173-175
40 ——— 1930 Experimental edema Further observations on the plasma proteins and blood cholesterol, Proc Soc Exp Biol Med, 27, 1002-1003
41 ——— 1931 Nephrosis, Medicine, 10, 135-242
42 ——— 1931 Experimental nephrotic edema, Arch Int Med, 48, 1-32
43 ——— 1931 The relation between the so-called renal lesions of plasmapheresis in dogs and contracted kidneys in man, Arch Int Med, 48, 280-300
44 Leiter, L, and McLean, F C 1929 Experimental edema, J Clin Invest, 7, 493-494
45 L [illegible] 1924 The concent
46 L
1924
in neph
47 Lyon, [illegible] the life of nephrectomized dogs with the production of edema, Arch Int Med, 44 424-437
48 McClure, C F W 1919 On the experimental production of edema [illegible] 1 261-267
[illegible] ödeme bei experi-
, 42, 250-2[illegible]
[illegible]sy, J Am Med
Assn, 48, 934-941
51 Meulengracht, E, Iversen, P, and Nakazawa 1 1928 Pernicious

anemia Edema and reduction in the excretion of water Arch Int Med, 42 425–439
52 Kobayashi Mozai et al quoted by Shimazono J 1927 Avitaminosen und verwandte Krankheitszustande Stepp W and Gyorgy P Berlin, p 601
53 Murphy F D and Warfield L M 1926 Lipoid nephrosis Arch Int Med 38 449–468
54 Nau, A 1928 Minéralisation des humeurs et des muscles dans des cases d oedème expérimentaux chez le lapin Compt rend Soc de biol, 99 869 872
56 Oehme C 1926 Grundzuge der Oedempathogenese mit besonderer ... d inn Med u

An experimental ... vascular injury

1927 Plasma ... malnutrition, J

Nierenwassersucht

Berl klin Wchnschr 42 384–387

100 ...–410

...opsy, Lancet ...
68 Stewart G T 1871 Practical Treatise of Bright s Disease of the Kidneys Edinburgh
69 Swingle W W 1919 On the experimental production of edema by ...

by paraphenylenediamine J Pharm and Exp Therap 24 179–211
72 Volhard Fr and Fahr T 1914 Die Brightsche Nierenkrankheit Berlin
73 Wolferth C C 1921 Inanition edema associated with alimentary ... merica 8 785–801
Robertson J D 1930 A study ... without proteinuria and its bearing

... f restriction of protein intake on serum protein concentration of the rat J Exp Med 57 705–720
76 ——— 1934 Effect of carrot feeding on serum protein concentration of the rat J Exp Med 59 687–698
77 Darrow D C Hopper E B and Cary M K 1932 Plasmapheresis edema I The relation of reduction in serum proteins to edema and the pathological anatomy accompanying plasmapheresis J Clin Invest, 11 683 699
78 ——— 1932 II The effect of reduction of serum protein on the electrolyte pattern and calcium concentration J Clin Invest 11 701–715

79 FAHR G LERKHOFF A AND GIERE E 1931 Salt as a factor in edema formation following plasmapheresis Proc Soc Exp Biol and Med 29 335-336
80 HOLMAN R L MAHONEY E B AND WHIPPLE G H 1934 Blood

Invest 11 621-639

Clin Inves 11

90 SHELBURNE S A AND EGLOFF W C 1931 Experimental edema Arch Int Med 48 51-69

CHAPTER XXXVI

EXPERIMENTAL EDEMA THE EFFECT OF LOW PLASMA-PROTEIN LEVEL UPON WATER BALANCE AS RELATED TO SPECIFIC IONS *

By M HERBERT BARKER M S M D

Introduction —In 1827 Bright* pointed out the relationship

ciency affected chiefly the albumin causing the ratio of the albumin to globulin to fall below unity Epstein[20] [1] found low proteinemia to be characteristic of those cases of chronic parenchymatous nephritis called nephrosis by Muller[34] Munk[33] and Volhard and Fahr[35] Epstein[2] considered the low protein level to be the result of the marked albuminuria and that it so reduced the colloid osmotic pressure that seepage of fluid into the tissues took place thereby causing the edema He suggested the feeding of a high protein diet to patients presenting albuminuria edema and low serum protein This regime brings about remarkable improvement in some ca es with disappearance of edema and return of the blood proteins to normal levels while in other cases it has been of no d monstrable help Other factors such as elimination of infected foci bed rest restriction of salt or the giving of various substances such as ammonium chloride calcium chloride ammonium nitrate urea thyroid extract pituitary extract hypertonic glucose and salyrgan have each at times apparently relieved edema after other means have failed

The appearance or disappearance of edema does not follow the plasma protein concentration as might be expected Linder Lundgaard and Van Slyke[31] did not find any close relationship between variations in edema and the plasma proteins although they felt certain that the albuminuria was an important factor in reducing the concentration of the plasma proteins The majority of their patients with small albuminuria exceeding 1 gm per day showed a reduction in the total protein and in the ratio of albumin to

* From the Departments of Medicine and Physiology Northwestern University Medical School

globulin These authors concluded with Epstein[22] that the clinical picture was an expression of an underlying metabolic disorder of a fundamental nature

The importance of the level of the plasma proteins in relation to nephrotic edema has been experimentally demonstrated by Leiter[30] and Barker and Kirk[7] These workers have produced nephrotic edema in dogs by the reduction of the plasma proteins by repeated plasmapheresis Their experiments support the original hypothesis of Epstein[21]

The process of removing large amounts of blood with the reinfusion of the cells after discarding the plasma is regarded as an adequate substitute for proteinuria If this process can be carried out over long periods of time chronic nephrotic edema so produced can be studied in detail under relatively well controlled conditions Such a study might be of help in interpreting clinical findings and suggesting therapeutic measures With this idea in mind an attempt has been made to ascertain more about the factors that influence the edema associated with low proteinemia

Method Six young adult dogs weighing 15 to 20 kg were selected and placed in metabolism cages They were fed liberally an adequate diet as given to dogs in the Department of Physiology at Northwestern University Chicago Ill This diet was maintained nearly constant it included about 1 2 gm of sodium chloride and 300 to 800 cc of fluid daily The dogs were given water *ad libitum* and the fluid intake and urinary output were recorded for twenty-four hour periods together with the body weight Two dogs were kept as controls while 4 were so trained during the preliminary observation periods that all procedures could be carried out without the use of sedatives or anesthetics Low proteinemia was produced and maintained by plasmapheresis[7] The dogs were bled the proper amounts which varied for each animal

The bleeding was accomplished by direct puncture of the femoral artery with a No 19 medium bevel needle As soon as the flow was established the needle was connected to a firm rubber tubing 15 inches long and attached to a right angle glass tube placed through a 2 hole rubber stopper and reaching nearly to the bottom of a 250-cc centrifuge bottle containing 15 cc of 10 per cent sodium citrate solution A short glass tube was placed in the other hole of the stopper and connected to a long piece of heavy rubber tubing This was connected to an air-suction apparatus so that moderate negative pressure could be maintained within the centrifuge bottle to facilitate bleeding With this method the removal of 500 to 1000 cc of blood could be accomplished by merely changing the stopper from one centrifuge bottle to another without clotting taking place in the needle Care was exercised to agitate the centrifuge bottle gently during the bleeding

The bottles were covered with rubber caps and centrifuged at 1000 r p m for twenty minutes The plasma was removed by suction through a small sterile glass pipette The red cells were diluted to their original volume

with Ringer's solution Another two hole stopper with its glass and [illegible]

[illegible]

[illegible] from the front leg [illegible] before plasma [illegible]

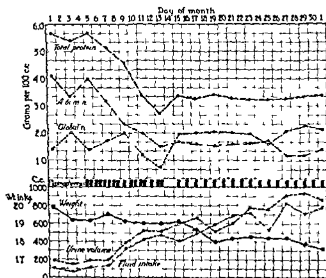


Fig. 129 Illustrating how the levels of the serum proteins the water intake and [illegible] increase of urinary output

Results. – The daily removal of 750 cc of blood with reinfusion of the cells after discarding the plasma resulted in a rather rapid lowering of the serum proteins If plasmapheresis was carried out

two or three times daily, the depression of the proteins was more quickly brought about This was shown by Dog 6 (Fig 129) When the serum proteins were reduced to about 3 5 per cent slight pitting edema of the legs scrotum and abdominal wall appeared In general this soft dependent edema increased if the vigorous bleedings were continued and disappeared within a few days *following the cessation of bleeding*

The first and important part of the problem was to produce a slight and constant edematous state as the basis for the study This condition was brought about by daily plasmapheresis in varying amounts until the proper volume was found necessary just to maintain the animals with slight pitting edema of the legs This was accomplished with difficulty in some animals and with ease in others As an example of the former Dog 3 required the removal of 38 000 cc of blood over a period of two months in order to produce a state of edema that could be regarded as constant After this time he was easily held on the edema margin by removal of 500 cc about four times a week As an example of the latter the total serum proteins of Dog 6 were reduced from their initial level of 6 3 gm to about 3 3 gm per 100 cc in a period of ten days by plasmapheresis of *8000 cc After this time slight edema was* present The edema and the serum protein level of about 3 3 gm were maintained quite constant by the daily removal of 450 to 475 cc of blood (Fig 129) This volume seemed to correspond to the amount of protein this particular dog could regenerate per day *

The level of the water balance showed marked changes during *the period of protein depletion and during the period of edema* maintenance There was a gradual increase of thirst as the serum proteins were reduced The animal frequently showed an increase of 500 to 800 per cent in the water drunk Urine volume increased in the same proportion and there was no water retention until the serum proteins were further depressed (Fig 129) No explanation for this elevation of the level of water metabolism is evident Dog 3 *showed the greatest increase of volume intake* He drank between 900 and 1100 cc per day during the control period and during the

* R[illegible] of [illegible] was very rapid as compared with albumin so that the

period when edema was maintained his intake and output gradually increased to 4500 or 5500 cc per day without any remarkable variation in weight
diet before the
the serum prot
800 cc per day

he had been carried under good control for the longest period of

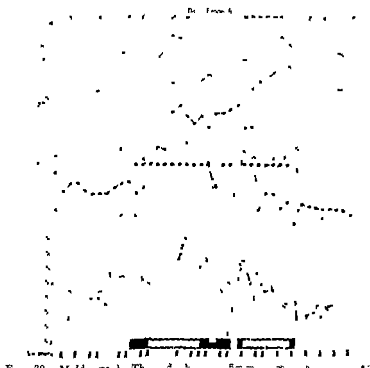
were on the whole about 1 5 per cent each and the urinary output of 4500 cc was essentially the same from day to day (Fig 130, lower graph) The average weight was about 19 5 kg and the chloride intake (the food contained about 1 3 gm NaCl daily) and the chloride excretion ran quite parallel (Fig 130 middle graph)

Sixteen gm of sodium chloride were then added daily to the water drunk by the dog Water and chloride retention immediately began and the body weight increased 53 per cent in five days By this time edema and ascites* were massive and the animal was able to get around only with difficulty Plasmapheresis was discontinued for three days and soon the chloride output began to
urine volume the
led on three suc-
the chloride and
urine excretion and the body weight rapidly increased to the previous level This sharp response of water and chloride excretion (Fig 130 middle graph fifteenth sixteenth and seventeenth days) following the cessation of plasmapheresis (twelfth thirteenth and fourteenth days) together with the equally marked reversal of the salt and water balance following the renewal of the bleedings (seventeenth eighteenth and nineteenth days) demonstrate the importance of the level of the serum proteins in this type of edema

Potassium chloride was then substituted for sodium chloride Sixteen gm of the potassium salt were added to the water which the dog drank readily Within a few hours an increase of the urinary output was evident A marked diuresis followed which caused

* The ascitic fluid had a protein content of 0 10 to 0 1 per cent which seemed to consist entirely of albumin The chlorides were 730 to 740 mg per 100 cc and the freezing point was 0.5 1° C

all the ascites and edema to disappear within three days The body weight dropped 5 5 kg in twelve hours and continued to fall



loss of the edema

until it reached a level below that of the foreperiod The dog showed an increased desire for water while the sodium chloride was given His intake gradually rose until he drank 9000 cc during

one day This huge intake occurred while he was retaining large amounts of salt and water (Fig 130) The fluid intake was well above the urinary output during this period As soon as the potassium salt was substituted for the sodium there was an apparent satiation of the thirst and the fluid intake quickly fell below that of the foreperiod The urinary output exceeded the intake by 500 to 2500 cc per day The chloride excretion rose sharply as the potassium salt was started but soon the calculated intake of chloride and the chloride excretion were about equal The chloride intake and output thus remained in equilibrium on a high level until the potassium chloride was discontinued following which the chloride

protein was below that determined at any previous time The

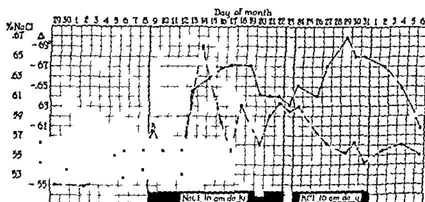
normally about 550 mg per 100 cc began to fluctuate and soon increased to about 640 mg (Fig 131) This increase was associated with chloride retention and the formation of edema as described

ing point of the serum showed a sudden depression coincident with the feeding of the sodium chloride There were some rather wide fluctuations in the freezing point readings but the average trend was downward (Fig 131) The control determinations were −0 55 to −0 56° C with gradual increase to −0 63° C As soon as the potassium chloride was started the freezing point gradually returned toward the normal It rose from −0 63° to −0 573° C in eight days Rather wide variations in the freezing point readings were obtained while sodium chloride was given The lowest value reached by the freezing point was −0 19° C This determination is rather far removed from the average readings but check determinations gave identical results This low freezing point was obtained while the greatest retention of water took place On the

whole there was no close correlation but the freezing point curve seemed to follow that of the body weight (Compare Figs 130 and 131) As edema decreased, the freezing point rose The

tween

freezing-point being nearest to normal when the blood chlorides were at their height *



of the plasma chlorides during the feeding of

The hydrogen-ion concentration of the blood showed considerable variation During the period of sodium chloride administration there was a gradual fall of the pH from 7 29 to as low as 7 13

the pH were not obtained during the control periods or after the salts were discontinued Although the results were not clear-cut, the hydrogen-ion concentration as determined was on the average, much increased during the period of chloride administration The

* Some of the discrepancies encountered between the different terminations are ... parallelism between

carbon dioxide combining power of the blood showed a rather sharp increase from 41 to 52 volumes per cent seven days after starting the sodium chloride. This elevation of the blood CO_2 continued until five or six days after the potassium chloride had been discontinued. On the whole, the blood pH was decreased and the blood CO_2 was increased (Fig. 13). No explanation was apparent for the late return of the carbon dioxide to its normal level.

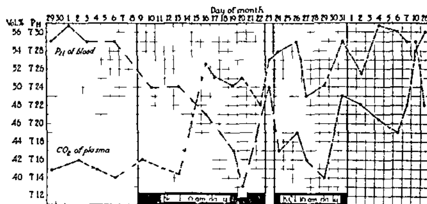


Fig. 13. Illustrates the blood pH and the plasma CO_2 changes during the period shown in the previous figures. There was an average decrease of the blood pH and a marked increase of the blood CO_2 combining power. Note the gradual elevation and delayed fall of the CO_2.

Discussion. The studies by Leiter and by Barker and Kirk have offered the experimental proof for Epstein's theory for edema as due to hypoproteinemia. Since Epstein's theory was proposed more attention than earlier has been given to the pathogenetic differentiation of clinical edema. The nephrotic edema for which Epstein's theory applies is differentiated at least on the American continent from the edema of acute nephritis. The earlier theories concerned themselves with the common edema of subacute and chronic nephritis. All the patients on whom the mechanism of edema was studied in the more important papers before Epstein

figured as leading symptom and based its explanation of edema upon the concept of hydremic plethora (Grainger-Stewart[22] and Bartels). Failure through huge intravascular injections experimentally to produce a water retention resembling the edema in Bright's disease demonstrated the insufficiency of this concept and

led Cohnheim and Lichtheim to assume an alteration in vascular permeability as the significant factor in nephritic edema (1877) Today Volhard on the whole adheres to this theory the same concept likewise forms a part of the theory of Achard

Though Hamburger [1] deserves the credit as the first to have called attention to the avidity with which a constant osmotic pressure is preserved in the body it was through the work of Korányi in the late 90 s that this idea became fruitful to clinical medicine and

workers Lemierre and Javal [40,41] when in their well known clinical experiment through the administration or withdrawal of sodium chloride they caused nephritic edema to augment or diminish as the chloride balance shifted between positive and negative according to the phase of the experiment Similar experiments with identical results at about the same time were carried out in Korányi s Clinic by Kovesi and Róth-Schulz

Seeing in the NaCl retention the chief cause of the edema Widal ascribed the retention to an inability on the part of the kidney to eliminate the salt while Achard assumes an alteration of the tissues as the cause of the salt retention and the edema

Attention might be called to two points in the experiments from this period In 2 patients 1 of Widal and Lemierre and 1 of Courmont the addition of sodium chloride to the diet besides increasing the edema also precipitated attacks of convulsive uremia The second point Neither in the experiments of Widal nor of Kovesi and Roth Schulz was there any parallelism between NaCl retention and weight gain the gain in weight falling far behind the retention as measured by the determination of the chlorides and calculated either as a solution of the chloride content of the plasma or of the concentration of a physiological saline solution

The occurrence of considerable edema in diabetic patients to whom large amounts of $NaHCO_3$ were given together with observations that in hydropic nephritics bicarbonate like NaCl will increase the edema (Blum) as is also the case in patients afflicted with hunger edema (Hulse Berglund) are all well known observations indicating the importance of the Na ion rather than the Cl ion

Hastings and Van Dyck through their discovery of the bromide edema and the demonstration of the complicated nature of its mechanism were able to shift the interest back to the importance of the anions

Bunge remembered for his discussion of the diverging dietary habits in the world s population especially in regard to the use of sodium and potassium was the first to demonstrate (1873) in careful experiments that ingestion of small amounts of potassium salts

might cause the elimination of considerable amounts of sodium chloride The proven diuretic action of various potassium salts (Bock Adolph) by Eichholtz and Starling[19] has been coupled with the simultaneous presence of excess of calcium, the mechanism for the effective combination of these two cations remain unexplained

Gamble as well as McQuarrie have correlated the potassium content of the cells and sodium content of the extracellular fluid with the urinary excretion of the same cations for the purpose of analyzing the origin of lost water in controlled experiments To summarize the composition of the fixed base under different conditions is assuming a position in pathology of increasing importance

Volhard in 1914 introduced the useful term Oedembereitschaft an expression which with a slight shift in meaning usually is rendered as tendency to edema

The experiment reported in this chapter on the basis of Epstein s theory and the experimental proof for the same rendered by Leiter and by Barker and Kirk in its long foreperiod offers one possible correspondence to the clinical stage of Oedembereitschaft In its NaCl feeding experiment it leads us back to the observations of the time of Widal but on the new basis of hypoproteinemia In its KCl experiment it again centers the interest upon the cations

Summary A method for the production and the maintenance of a nephrotic type of edema is described An increased thirst was associated with reduced serum proteins but there was no retention of water in the tissues until the serum proteins were reduced to 3 or 3 5 per cent Factors that influence water balance may be successf[illegible]
type of [illegible]
edemato[illegible]
reduced seru[illegible]
sodium chlo[illegible]
water balanc[illegible]
has been of [illegible]
their edema These experiments further point toward the importance of the sodium ion as a factor of significance in the formation of edema More rigid dietary control of edematous patients reducing the sodium and increasing the potassium intake is indicated The chlorine ions play a less important role It is suggested that in nephrotic edema the restriction of water probably will not greatly influence the underlying cause of the edema It appears that the increase of the serum protein and the restriction of the sodium ion are the factors of greatest importance in the control of nephrotic edema

REFERENCES

1 Abel, J J 1915 Experimental and clinical studies of the blood with an appeal for more extended clinical training for the biological and medical investigator Science 42 135–14[illegible]

2 ACHARD CH 1901 Le méchanisme régulateur de la composition du

31 611–615
7 BARKER M H AND KIRK E J 1930 Experimental edema (nephrosis) in dogs in relation to edema of renal origin in patients Arch Int Med 45 319–346
8 BARTELS C 1875 Handbuch der Krankheiten des Harnapparates I Leipzig
9 BERGLUND H 1920 Studier over koksaltomsattningens fysiologi och

48 358–368
18 CULLEN G E 1922
ion concentration of blood plas
19 EICHHOLTZ F AND STA
salts on the secret on of the isc
20 EPSTEIN A A 1913
J Exp Med 17 444–452
21 ——— 1917 Concerning the causation of edema in chronic parenchymatous nephritis methods for its alleviation Am J Med Sci 154 638–648
22 ——— 192
chronic nephrosis Am J
23 GRAINGER STEWART
of the Kidneys Edinburgh
24 HAMBURGER H J 1890 Ueber die Regelung der Blutbestandtheile bei experimenteller hydramischer Plethora Hydramie und Anhydramie Ztschr f Biol ns 9 259–308
25 HARVEY S C 1910 The quantitative determination of the chlorides in the urine Arch Int Med 6 12 18
26 HOWE P E 1921 The determination of proteins in the blood a micro method J Biol Chem 49 109 113
27 HULSE W 1918 Untersuchungen ueber Inanition oedeme Virchows Arch f path Anat 225 234–283
28 KOCH F C AND MCMEEKIN T L 1924 A new method (direct he Nessler Folin reagent

ologie und Therap e
eme
Exp Biol and Med

26 173 175

31. LINDER, G. C., LUNDSGAARD, C., AND VAN SLYKE, D. D. 1924. The [illegible]

36. VAN SLYKE, D. D. 1917. A method for the determination [illegible] J. Biol. Chem. 30: 347-368.

[illegible] hämatogenen Nierenerkran-

[illegible] Brightsche Nierenkrankheit,

PART V

OCULAR CHANGES IN BRIGHT'S DISEASE

CHAPTER XXXVII

RETINAL LESIONS IN NEPHRITIS AND HYPERTENSION

By HENRY P WAGENER M D

RETINITIS IN NEPHRITIS

Lesions in the retina in cases of nephritis vary considerably in type and their exact relationship to the general features of the disease is often not obvious In the main when retinitis is present definite retention of urea will be found But retinitis does not always accompany renal insufficiency and apparently it has no direct relationship to the presence or the degree of retention of urea

nephritis Lesions in the retina are rare in the other varieties of nephritis (From the retinal standpoint the arteriolosclerotic kid ney is considered as a part of the picture of essential hypertension)

In cases of *nephrosis* retinitis is never seen Occasionally in the presence of marked generalized edema slight edema of the retina may be suspected but the author has never seen it sufficient in degree to justify a definite diagnosis The retinal vessels are always normal in pure nephrosis The development of arteriolosclerosis should always suggest that an evolution of the nephrosis into glomerulonephritis has taken place In cases of nephrosis in which there is an increased concentration of blood fats the blood in the retinal vessels may have a slightly creamy tint But this lipemia retinalis is always mild and transitory

In *focal nephritis* the fundus is normal In cases of *ascending pyelonephritis* of severe grade occasional usually single hemor rhages or cotton wool patches may be found in the retina But these may be seen in general toxemia or septicemia from any source and are not characteristic of the renal disease and are not related to the degree of renal insufficiency

Sclerosis of the retinal arterioles is seen at times in association with *polycystic kidneys* This sclerosis is of the usual type seen in essential hypertension and when retinitis occurs it is not distin guished from the retinitis of severe essential hypertension It is ret

initis of hypertensive disease and not retinitis of nephritis although the hypertension probably arises as a sequel to the renal lesion

Glomerulonephritis is the only variety of nephritis in which retinitis is at all common. The retinitis of chronic glomerulonephritis commonly designated albuminuric retinitis is characterized by anemia and edema of the disk, generalized usually rather dense grayish white edema of the retina visible especially for 3 or 4 disk diameters around the disk ("snow bank exudate"), hemorrhages and occasional cotton wool patches superimposed on the edematous retina and in the macular region the radiating star figure made up of rather large thick groups of irregularly shaped hard white

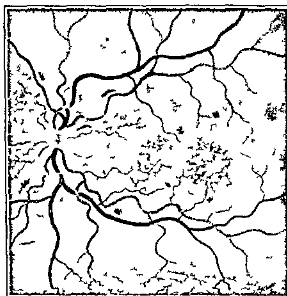


Fig 133 Retinitis of chronic glomerulonephritis

exudate. The vessels, especially the arterioles, are difficult to distinguish because of the surrounding edema but they often appear narrowed and sclerosed (Fig 133).

The picture which is the one usually given is really that of a late stage of the retinitis. In the most typical cases the outstanding feature of the early stage is generalized edema of the retina. Vascular changes are not striking. There is likely to be generalized constriction of the arterioles but no definite sclerosis. The edema fluid is at first of watery consistency and its presence is difficult to recognize except through blurring of details. A few flame-shaped hemorrhages are usually scattered through the retina. The edema gradually becomes more extensive and the fluid of denser

albuminous appearance It is often sufficient in amount to cause detachment of the retina The spots arranged around the macula as the 'macular star' are formed in the process of absorption of the edema fluid and therefore indicate that the edema is receding They are not characteristic of nephritis but are found in edema from any cause if the edema involves the macular region In less typical cases in which hypertension and generalized vascular disease have become the most outstanding features of a long standing *chronic glomerulonephritis* the retinitis is associated with sufficient evidences of arteriolosclerosis to resemble closely the retinitis of malignant hypertension Patients with chronic glomerulonephritis rarely live long enough after the development of retinitis to allow the retinitis to heal completely If the retinitis does subside however the end picture is that of any retinitis of edematous or vascular origin pallor with some blurring of the disk secondary arteriolosclerosis and atrophy and degeneration of the retina with proliferation and clumping of pigment especially in the macular region and periphery The arteriolosclerosis which follows retinitis is different from that seen in hypertensive disease without retinitis and is characterized by irregular narrowing of the vessels with loss of transparency of the walls and perivascular thickening and infiltration involving the veins as well as the arterioles

This typical albuminuric retinitis is seen most commonly in the *terminal stages of chronic glomerulonephritis* Its evolution can be watched more readily however in cases in which the condition passes from acute nephritis with little if any quiescent period *into a subacute phase with progressive renal insufficiency* In acute glomerulonephritis as ordinarily seen retinal changes are not found Perhaps in most cases mild retinitis develops at the onset and is characterized by mild hyperemia or ischemia of the disk, some arteriolar constriction mild edema of the retina and a few flame-shaped hemorrhages in the vicinity of the disk (acute angiospastic retinitis) This retinitis however may last only a few days and may leave only slight residuals thus the majority of patients with acute nephritis will show normal fundi The fundi remain normal until the terminal stage of the nephritis is heralded from the ocular standpoint by the usually sudden appearance of retinitis During the quiescent period no changes in the arterioles are visible by means of the ophthalmoscope The retinitis then develops without preceding arteriolosclerosis and is *distinguished by this fact* from the retinitis of primary hypertensive disease Constriction of the arterioles is usually apparent at the onset of the retinitis The *primary changes in the retina itself* are edema and hemorrhage Part and at times most of the edema is subretinal While this retinitis is most often of angiospastic origin edema of the retina is associated in some cases of severe generalized edema and may be

in part at least of the same origin as the general edema. In such cases it shifts as does the general edema, with the position of the patient in bed and can be markedly increased if the head is lowered, and decreased if the head is elevated. This is not true of edema of the fibrinous stage or type usually seen in 'albuminuric' retinitis.

In subacute glomerulonephritis the retinitis is often as severe as it is in chronic glomerulonephritis. In some cases however a

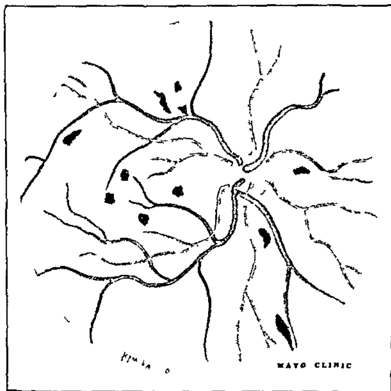


Fig 134 Retinitis of subacute glomerulonephritis.

much milder form is seen with only slight edema of the retina and a few cotton wool patches and hemorrhages. Such retinitis is indistinguishable from that of severe benign hypertension except by the absence of arteriolosclerosis (Fig 134).

In most cases of chronic glomerulonephritis the retinitis is of the edematous or vascular type just described. In some cases, however from the standpoint of the retina the secondary anemia associated with the renal insufficiency seems to be the dominant

factor In such cases mild retinitis will be seen hardly distinguishable from that found in pernicious anemia or in anemia secondary to carcinomatosis The disk is definitely anemic and scattered superficial cotton wool patches and hemorrhages usually of the irregularly round type with white centers characteristic of anemia are found in a slightly edematous retina The retinal arterioles are likely to be constricted instead of dilated as they are in the other types of anemia This is the main distinguishing feature

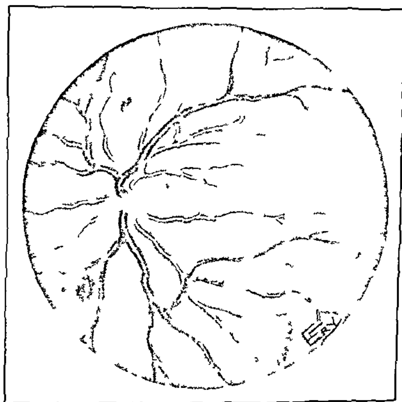


Fig 135 Retinitis of anemia in nephritis

and is not constant It is dependent probably on the elevation of the blood pressure Retinitis of this type is seen *only in cases* in which the secondary anemia is severe and in which the concentration of hemoglobin is less than 40 per cent (Dare) It is not clear why this retinitis develops in place of the typical retinitis of nephritis (Fig 135)

In most cases of primary glomerulonephritis there is not any visible sclerosis of the retinal arterioles prior to the onset of retinitis

The arterioles become sclerosed in the course of the retinitis but the residual sclerosis seen after the subsidence of the retinitis in the rare cases of recovery is essentially secondary to the retinitis I ... es in which there is persistent hypertension with associated r ... following acute nephritis the residual lesion ... lar disease rather than ... elops ... b ... ire ... is ... out ... tis

of arteriolosclerosis is never a ...

Retinal arteriolosclerosis is ... which complicates t... only of the diffuse vascular disease which occurs in the various phases of glomerulo-

That the retinitis which occurs in the various phases of glomerulonephritis is not dependent on preceding arteriolosclerosis is clinically obvious. The theory is at least alluring that it is the result of vasoconstriction or vasospasm with capillary ischemia or stasis. A number of observers have demonstrated rather conclusively that spasm does occur in the retinal arterioles. Spasm of individual arterioles as seen in cases of recurrent transitory obscuration of vision is characterized by sudden complete wiping out of the vessel beyond the point of spasm. If such a spasm disappears promptly as it usually does there is no residual injury. If it ... eral hours or days the retina degenerates and loss ... pplied by the affected arteriole ... ly beyond the point ... pasm with resultant ... ceivably produce the

of spasm. Less c... circulation ... interference in capillary circulation ... of as retinitis. Tox edematous and hemorrhagic changes spoken of as retinitis. Toxemia of pregnancy affords the best opportunity for studying the effect of persistent non-obliterating spasm of the retinal arterioles.

In t*oxemia of pregnancy* the retinal changes suggest acute vascular disease rather than glomerulonephritis. In this or hypertensive disease the effects of acutely or rapidly rising hypertension are best seen. The first visible sign is constriction of the arterioles definitely spastic in type. The constriction does not involve all the vessels uniformly and its intensity varies at different points in the course of the same arteriole. An appearance of irregular constriction is produced which is similar to that seen in arteriolosclerosis. It may be interpreted as sclerosis if the patient is seen for the first time in the stage of tonic contraction. But these constrictions are really spasms and if carefully watched in the early stages they will be seen to shift their situation in the vessel and to change in degree of constriction as well as in position. Complete obliteration of the arteriole beyond the point of spasm never occurs. If the toxemia persists these varying spasms become tonic and fixed and if constriction is sufficiently severe edema hemorrhage and exu

dation appear in the retina usually *in definite association with the* visible points of maximal constriction Such retinitis is similar to that seen in severe but not malignant hypertensive disease the main difference is that the disk is more anemic or ischemic in appearance and is more likely to be mildly edematous (Fig 136)

In certain cases the spastic constriction seems to involve the central artery as well as or rather than individual retinal arterioles

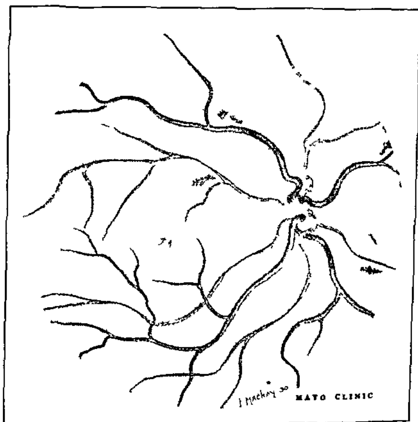


Fig 136 —Retinitis in toxemia of pregnancy

and *retinitis results which is like that of glomerulonephritis* with edema and anemia of the disk and generalized edema of the *retina* with superimposed cotton wool patches and hemorrhages The arteriolar constriction and the retinitis of toxemia of pregnancy usually subsides fairly promptly after delivery the residual injury varying with the severity of the retinitis If delivery has taken place while the spasms of the arterioles are still varying or clonic in nature, the arterioles rapidly return to normal If the spastic

constriction of the arterioles has been allowed to persist to the point of inducing edema of the retina the resultant ischemia of the vascular wall or the perivascular edema or both cause permanent injury or sclerosis of a grade dependent on the severity of the constriction or of the retinitis Evidently similar injury occurs

portionate to the grade of the retinal arteriolosclerosis A patient for example who entered the hospital with toxemia of pregnancy and severe retinitis had residual sclerosis of the retinal arterioles

losclerosis For the future well being of the patient pregnancy should be interrupted at the first signs of tonic arteriolar spasm with localized edema

Haselhorst and Mylius[1] expressed the belief that the edema of the retina in toxemia of pregnancy results from capillary stasis in the region of maximal arteriolar constriction They were able to demonstrate stasis in the capillaries of the nail fold coincident with maximal spasm of the retinal arterioles Convulsions occurred shortly after this stage was reached

In a few cases of toxemia of pregnancy the circulatory disturbance seems to involve mainly the choroidal vessels In these cases anemic or ischemic foci appear in the choroid as scattered pale washed-out round patches These may represent spasms of choroidal arterioles Following these generalized progressive subretinal edema develops with resultant detachment of the retina which may become total Lesions in the retina proper may be minimal A similar sequence of events may be seen at times in subacute glomerulonephritis Such detachments usually disappear rapidly after delivery with much less residual injury than would be expected from a typical retinitis similarly severe in degree There is only slight if any residual sclerosis of the arterioles of the retina In such cases the blood pressure usually returns to normal rapidly The author has seen one patient who went through two succeeding pregnancies without return of the hypertension or of the toxemia

RETINAL LESIONS IN ESSENTIAL HYPERTENSION

Sclerosis of the Arterioles In [illegible]

ently arterioles which measure 60 μ or less in diameter They share therefore in the general *involvement of the arterioles throughout the body* As seen with the ophthalmoscope the first alterations that take place in the arterioles of the retina are narrowing *of the caliber a change to a lighter color than normal of the entire* breadth of the arteriole and exaggeration and broadening or accentuation of the reflex stripe These are regarded by some as signs of hypertension in the sense of spastic arteriolar constriction or increased arteriolar tonus and by others as the commencement of actual arteriolosclerosis through thickening of the media In more advanced cases signs of definite sclerosis appear irregularities of the lumen of the arterioles compression of the veins at the arterial crossings and at times visibility of the vascular walls Irregularity of lumen is the most definite sign of sclerosis if it is not confused with the irregularity produced by spasm Severity *of sclerosis can be graded from 1 to 4 largely on the basis of the* number of irregularities and the degree to which they narrow the lumen of the arterioles Sclerosis observed in advanced cases is visible in all branches but in earlier stages is best seen in the smaller arterioles either in the nasal or in the secondary and tertiary branches of the temporal vessels It is usually rather evenly distributed in grade in all vessels of approximately the same size As has been mentioned a certain amount of visible thickening of the vascular wall may occur in some cases but in the main definite perivascular infiltration is seen only when retinitis with edema of the retina has been present previously Primary periarterial and perivenous thickening occurs more often in inflammatory disease of the vessels such as that seen although rarely in vascular syphilis or tuberculosis

In the senile retina the arterioles are attenuated but do not have the burnished color which indicates constriction or thickening of the media When hypertension is present in cases of this senile type of retina there is also a certain degree of irregularity of lumen in the attenuated arterioles The veins are usually narrowed as well and there is no arteriovenous compression This senile sclerosis is rarely more than Grade 1 or 2 in severity It is more common than the ordinary variety seen in hypertension in persons who are more than sixty years of age and who have mild essential hypertension and coronary sclerosis

When sclerosis of the hypertension type has developed it remains obvious in the retina even though the blood pressure falls Its presence therefore even in mild degree is of diagnostic value in cases of cardiac decompensation since it indicates even if the blood pressure is normal or low that the cardiac disease is entirely or in part on a basis of hypertension This has been proved by

the clinical studies of O'Hare and Walker[3] and by the clinical and postmortem studies of Kater and Wagener[5]

In mild practically non progressive hypertension there is little if any visible increase from year to year in the sclerosis of the retinal arterioles It will be found to be graded the same on re peated visits If the sclerosis is found to increase definitely in grade as the patient is kept under observation it can be assumed that the hypertensive disease is progressive From time to time small hemorrhages may be seen in the retinas of such patients The e do not mean necessarily that the disease is not relatively benign and they are not indicative of renal insufficiency They have no more serious significance than the degree of arteriolosclerosis with which they are associated but they do indicate that the hypertension is of progressive type

Retinitis Exclusive of sclerosis the lesions which occur in the retina in cases of hypertension and which are described under the

is which have

The lesions

efully distin

guished from those due to another feature of the systemic disease which formerly was presumed to be renal insufficiency but which is more probably angiospasm To the group dependent on arteriolosclerosis belong thrombosis of the retinal veins and the retinitis of arteriosclerosis To the angiospastic group belong the retinitis of severe benign or intermediate hypertension the retinitis of malignant or fulminating hypertension and acute angiospastic retinitis

Even in benign non progressive hypertension sclerosis of the retinal arterioles not necessarily of high grade may be complicated by *venous thrombosis* Thrombosis of the central vein of the retina or of one of its branches is usually unilateral and in the latter case the edema hemorrhage and exudation are confined to the area of the retina drained by the thrombosed vein Recent thrombosis of the central vein is

cyanosis of the veins

the periphery of the re

as a rule only in the later stages In thrombosis of a branch vein the obstruction to the circulation occurs most often at an arterial crossing and careful search usually will reveal the portion of the vein central to the point of obstruction to be empty and the dilated and cyanotic distal portion to be hidden under more or less massive hemorrhages (Fig 137) The diagnosis is even more readily made in the later stages when the edema has subsided and the hemor rhages are being absorbed Healing takes place either by canaliza tion of the obstruction or through the establishment of anastomotic circulation by the formation of tortuous new channels or the dilata

tion of previously existing small channels of communication with other veins Hemorrhages will recur over a long period unless the anastomotic circulation is competent The degree of healing may furnish an index of the flexibility of the general vascular system

In a certain number of these cases of venous thrombosis the end result is a picture not unlike that of the retinitis of arteriosclerosis



FIG 137 —Recent thrombosis of the inferior retinal vein

described by Moore [2]
crete hard looking pi
vicinity of small term
may be found in any portion of the retina but they are usually confined to one area and not generalized throughout the retina Typically they are associated with rather severe arteriolosclerosis and are the result of the local obliterative vascular lesion From the standpoint of general diagnosis and prognosis therefore they are

no more significant than the arteriolosclerosis itself. The *retinitis of arteriosclerosis* is often unilateral. It is relatively rare and indicates a tendency to cerebral hemorrhage rather than to terminal renal insufficiency. Because of its different mode of origin and its different prognostic significance it should be distinguished from those varieties of retinitis which are dependent on the vasoconstrictive rather than on the sclerotic element of the hypertensive disease (Fig 138).

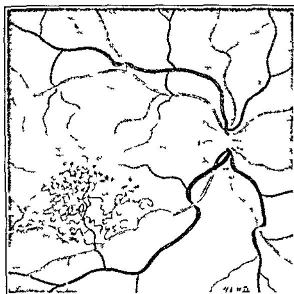


Fig 138 Retinitis of arteriosclerosis

The *retinitis* which is most *characteristic of hypertensive disease* is basically angiospastic and not angiosclerotic. It is associated with arteriolosclerosis but its severity is by no means proportionate to the grade of the sclerosis. The grade of the sclerosis may serve as

such retinitis always means that the hypertension is of progressive type. But it is possible to divide cases of hypertensive disease and angiospastic retinitis into two groups, severe benign or inter

The retinitis of severe benign or intermediate hypertension is characterized by hyperemia of the disks moderate constriction of the arterioles that is greater in spots varying grades of arteriolosclerosis and scattered cotton wool patches and hemorrhages in the retina Mild generalized or localized edema of the retina may be present in the early stages and may leave in the later stages scanty feathery white punctate residues This type of retinitis tends to clear up rapidly under proper treatment of the hypertension and the hypertension usually can be well controlled for a number of years The retinitis tends to recur however as the hypertension

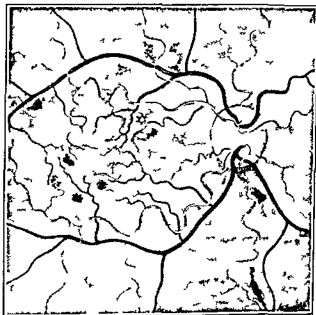


Fig 139 —Retin s of severe ben gn hypertension

progresses In the recurrences edema of the retina is likely to be more def
of the m
is never
The hypertensive disease in cases of retinitis with measurable edema of the optic disks is almost invariably of a rapidly progres sive and fatally
the term
malignant
pathognomonic
of the retinitis proper which is diagnostic The sclerosis is often less marked than in the retinitis of arterioscleros s or in that of

severe benign hypertension, and there is often comparatively little

hemorrhages are also present in the later stages, the smaller, feathery white spots characteristic of receding edema appear, especially in the macular regions with the formation of partial or complete macular stars In this stage the early constriction of the arterioles may be replaced by secondary relaxation and clumping of pigment

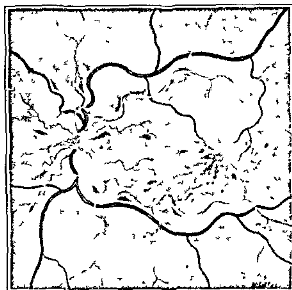


Fig 140 —Retinitis of malignant hypertension

in the choroid and the retina may be seen as the edema recedes from the periphery *In some cases however the lesions in the* retina are so minimal that it is necessary to depend on the condition of the arterioles to distinguish the edema of the disk from the choked disk of cerebral tumor The edema of the disk in these cases of malignant hypertension may be due in part at least to increased intracranial pressure since the pressure of the spinal fluid is found to be increased in the majority of the cases and the edema has been found to recede in some after spinal drainage (Fig 140)

As a rule the retinitis of malignant hypertension persists for the duration of the patient s life In a few instances however, it

subsides although the patient continues his downhill course In such cases the edema of the disk is the most persistent feature The end picture is a full pale disk with blurred margins a high grade of sclerosis of the retinal and choroidal arterioles usually with secondary perivascular deposits and atrophy of the retina and choroid with clumping of pigment especially in the macular region and periphery The picture is not unlike that seen after severe retinitis accompanying toxemia of pregnancy

The general prognosis is as serious in the case of healed retinitis as in persistent retinitis Few of these patients will live more than eighteen months to two years after the retinitis has been observed and the majority die in a much shorter time The retinitis is not confined to any age group It occurs in children aged less than ten years and in persons aged more than sixty years but it is seen most often between the ages of forty and fifty five years Most of the patients will have terminal renal insufficiency The retinitis is often seen however and the patient may die while renal function is still good The retinitis obviously is not dependent therefore on renal insufficiency The striking constriction of the arterioles in all the early cases often in the presence of minimal sclerosis especially in children seems to justify the interpretation of this

nsion is of the albuminuric
ts to the retinitis of chronic
glomerulonephritis The edema of the retina is less likely to be of the dense white coagulating type and detachment of the retina is less common Individual cotton wool patches are a more outstanding feature Most important however is the presence of arteriolosclerosis of the hypertension type which is absent in the early stages of the retinitis of glomerulonephritis In cases in which the edema of the retina is not sufficient to mask the arterioles differential diagnosis on this basis is comparatively easy If the arterioles are concealed by edema or if they are the site of perivascular thickening and sclerosis secondary to edema it is often difficult to be sure of the presence or absence of preexisting hypertension sclerosis and hence to distinguish definitely between the retinitis of malignant hypertension and that *of chronic glomerulonephritis* Careful study of the smaller arterioles in the less edematous periphery of the retina may make possible a correct diagnosis The color of the disks often is helpful in the differentiation of these *cases* *The disk in chronic glomerulonephritis* usually is pale because of the secondary anemia associated with the renal insufficiency The disk in malignant hypertension always is hyperemic except in the fourth or healed stage of the retinitis when secondary atrophy of the nerve has occurred

Acute Angiospastic Retinitis —In some cases of rapidly rising blood pressure in *acute nephritis* or in *diffuse vascular disease*, a retinitis occurs which is characteristically angiospastic but which in its early stages shows no organic lesions in the arterioles and no definite choking of the disks In acute nephritis and in a few cases of diffuse vascular disease this retinitis may subside with little or no residual arteriolosclerosis In most cases of diffuse vascular disease however arteriolosclerosis soon develops and its character, together with the course of the retinitis will often indicate the severity and prognosis of the general vascular disease In the acute phase of the retinitis an active lesion of the intima of the arterioles may be evidenced by the occurrence of thrombosis in one or more small arterioles Such cases usually progress rapidly to a fatal termination In a few however the retinitis subsides leaving only a residual arteriolosclerosis with obliterated small arterioles

sion in the

the retinitis

of the arterioles and choking of the disks develop In these cases the hypertensive disease runs the characteristic malignant or fulminating course

REFERENCES

CHAPTER XXXVIII

THE PATHOLOGY OF THE OCULAR CHANGES IN NEPHRITIS AND HYPERTENSION

By JONAS S FRIEDENWALD A M M D

Introduction The Pathogenesis of Albuminuric Retinitis —The history of thought in regard to the pathogenesis of albuminuric retinitis exhibits marked fluctuations pendulum swings characteristic of the slow advance of knowledge That visual symptoms occurred in the course of chronic nephritis was recorded by Bright[3] in his classical treatise The fathers of modern ophthalmology von Graefe and his pupils described the ophthalmoscopic appearance of albuminuric retinitis and named it We now recognize that it is not an inflammatory condition that the term retinitis is a misnomer and that albuminuria is only indirectly connected with the retinal lesion Still the old name remains in common usage and answers the purpose of attaching a label to a clinical entity

The first important anatomical investigations in this field were

to whom we are indebted for the first comprehensive study of the relation of retinal arteriosclerosis to general vascular disease led to the general acceptance of the notion that albuminuric retinitis is chiefly a vascular affection In 1907 Schieck[31] demonstrated sections from 2 cases of marked albuminuric retinitis in which he had been unable to find any serious vascular lesions This led to investigation of other possible causes of the retinal affection In 1903 Widal[35] and Rochon Duvigneaud and Opin[29] advanced the theory that the retinitis was a toxic affection produced by non protein nitrogenous substances retained in the blood This theory met with wide approval and was accepted by Leber[24] in 1909 but growing clinical knowledge soon revealed that nitrogen retention occurs in uremia due to urinary obstruction just as much as in chronic nephritis but retinitis does not occur in uremia of urinary obstruction Direct toxic action upon the retinal nerve elements from retained nitrogenous waste products or from some unknown toxin of hypertension or arteriolosclerosis has never been demonstrated The modern theory of the vascular basis of albuminuric retinitis seems an adequate explanation without the aid of hypothet

ical toxins This does not exclude the possibility of a toxic effect The question remains open

Cohen[8] in 1922, drew attention to changes in the blood vessels in the choroid in albuminuric retinitis and somewhat cautiously, suggested that the cause of the retinal affection might lie there An extensive study by Wood[10] on choroidal arteriosclerosis had already shown that changes in these vessels are extremely common in late middle life even in the absence of general arteriosclerosis The changes found by Cohen in albuminuric retinitis do not appear to exceed those found in the choroid in otherwise normal persons The author s experience fully confirms the findings of Wood In respect to vascular changes the choroid resembles the spleen showing marked sclerotic change in almost every individual over fifty years of age quite irrespective of the presence of general arterial disease

Another suggestion is that of Hanssen and Knack[18] who in 1917

arterial inflammatory nodules in the choroid in some instances with in others without albuminuric retinitis They concluded that the retinitis is an inflammatory lesion In the seventeen years *since the publication of Hanssen and Knack s paper 4 cases have* been reported showing inflammatory lesions similar to those described by these writers Three of these were cases of generalized periarteritis nodosa—2[14, 15] without and 1[16] with albuminuric retinitis One additional case of chronic nephritis albuminuric retinitis and terminal Streptococcus viridans septicemia showed the same lesion[16] One is forced to conclude that Hanssen and Knack were misled by the concurrent presence of some infectious disease Many of their cases were instances of trench nephritis while others suffered from relapsing fever

Volhard[36] has attributed the retinal lesion to vascular spasm with resultant retinal ischemia This theory is not subject to direct proof but is indirectly supported by the report of Schieck and others who were unable to discover morphological evidence of vascular disease in some cases of albuminuric retinitis

New light was thrown on the subject by Verwey[35] who used frozen sections and fat stains in the study of his cases He found in all cases of albuminuric retinitis evidence of arteriolar sclerosis in the retina The characteristic picture is that of a hyaline thickening of the arterial wall the hyaline containing large amounts of some as yet unidentified lipoid which stains deeply with Scharlach R and allied dyes He examined a considerable number of cases of general and cerebral arteriosclerosis and found that in no instance was there arteriolar sclerosis of the retina

The incidence of retinal arteriolar sclerosis in vascular and renal disease is of interest As stated above it does not occur in senile arteriosclerosis in which atheromatous lesions are most prominent It occurs almost invariably in general arteriolar sclerosis no matter whether the kidneys show marked lesions or not With equal frequency it occurs in arteriolosclerotic nephritis in some instances of which the kidneys and retinæ alone of all organs show marked arteriolar lesions Finally it occurs in many cases of chronic arteriosclerotic nephritis and of chronic glomerulonephritis even when there are no arteriolar lesions in the kidneys or in any other organ We are forced to conclude that the retinal arterioles are especially susceptible to damage by that agent as yet unknown which is the cause of arteriolar sclerosis

All forms of progressive renal degeneration may be complicated by retinitis or fail to show such lesion However a comparison of the kidneys of retinitis cases with those of progressive renal disease without retinitis reveals on the average more polymorpho nuclear infiltration and other evidence of active kidney destruction in those cases with retinitis than in those without it It is difficult to estimate such matters quantitatively but the study of a considerable series of such kidneys has led the author to believe that the rate of destruction of the kidney parenchyma and the concentration of Volhard s vasopressor (vasotoxin?) is intimately connected with the development of the retinitis This is in accord with the clinical fact that renal function goes rapidly down hill when or soon after the retinitis develops

Retinal Changes —In view of the importance of retinal arteriolar disease in the pathogenesis of albuminuric retinitis it is necessary to digress for the moment to discuss the nature of retinal vascular disease in general and especially the morphology of the structural changes recognizable with the ophthalmoscope upon which clinical diagnosis is based These ophthalmoscopically visible changes are the following

1 Beading of the vessels localized variations in caliber
2 General constriction or dilatation of the arteries
3 Arteriovenous constriction
4 Increased visibility of the vessel walls
5 Copper wire and silver wire vessels
6 Changes in the light reflex over the vessel

ANATOMY OF THE RETINAL VESSELS

Before entering upon the morphological basis for these ophthal

circumstances the retinal vessels are called upon to sustain an internal pressure approximately equal to that sustained by vessels of equal size in other organs. The pressure in the terminal arterioles is perhaps somewhat higher than the average because the capillary pressure in the eye is higher than in any other organ barring the effects of gravity. The gradient of pressure fall from the central retinal artery to the capillaries must, therefore, be somewhat less than in other organs.* The intraocular vessels, however, are aided in supporting their internal pressure by an external pressure of some 20 mm. Hg, namely, the intraocular pressure. On account of the high capillary and venous pressure within the eye the relief which the intraocular pressure gives to the vascular tree is manifested mainly in regard to the larger arterial branches. It is perhaps as a response to this relief from internal strain that the unusual delicacy of the retinal arterial wall is to be understood. This delicacy of structure may explain the unusually great local effects of changes in blood pressure if these local effects are truly disproportionate to those in other organs and not merely more easily recognizable. The retinal artery in its course through the orbit and optic nerve has a thick muscular coat similar to that of other vessels of similar size, but on passing through the cribriform plate into the eye the arterial coat abruptly dwindles to about one third its previous thickness. The intima remains unchanged, the elastic lamella is at first preserved, somewhat reduced in density, but disappears from the secondary or tertiary arterial branches in the retina, the adventitia becomes thinner and looser in structure. The greatest change in the vessel on entering the eye is in the media, which becomes reduced to a thin layer usually less than one-tenth the diameter of the vessel in thickness. It is difficult to demonstrate histologically the presence of smooth muscle fibers in the media of the retinal arterial branches. That contractile elements are present is undoubted on clinical and experimental grounds. On account of the thinness of the retinal arterial walls and their considerable variation under normal conditions, and also on account of the difficulty of estimating the functional internal diameter of collapsed retinal vessels seen in microscopic sections, minor changes in thickness of the arterial walls are difficult to recognize on microscopic examination. In the larger arterial branches in the retina the intima is sufficiently developed to allow atheromatous degeneration similar to the changes in larger arteries in arteriosclerosis. These vessels may also show hyaline degeneration of the media characteristic of arteriolosclerosis. It is of no interest whether these vessels are arteries or arterioles. The important fact is that they are capable of partaking differently in two different disease processes of

* For a thorough discussion of the intraocular vascular pressure the reader is referred to an article by Duke-Elder.[3]

the vascular tree and that therefore the careful clinical study of these different forms of vascular degeneration in the retina is of importance diagnostically and prognostically

A further peculiarity of the retinal vascular tree is the crossing of the retinal arteries and veins The retinal vessels excepting only the finest twigs and capillaries are spread out in a two-dimensional plane with the result that the arteries and veins are brought into intimate contact with one another at points of crossing In other organs the large arteries and veins often lie in a common sheath like the central retinal vessels in the optic nerve, while the smaller twigs of the arteries and veins branch apart and have no connection with one another except through the capillaries An exception to this rule outside of the retina is found in the afferent and efferent vessels of the kidney glomerulus Whether this fact is significant in the physiology and pathology of the kidney the author leaves to other participants in this volume



FIG 141 Arteriovenous crossing in the retina Vein above the artery

The histology of the retinal arteriovenous crossings has been studied carefully by Koyanagi[20] At the points of crossing the vessels have a common adventitia which surrounds them without extending into their wall of contact Here the media of the artery is in direct contact with the inner layers of connective tissue of the venous wall so that it becomes impossible to say where one begins and the other ends The total thickness of this common wall is not significantly greater than the arterial wall alone at other points The consequences of this intimate binding together of arteries and veins will be discussed in regard to the so called arteriovenous constriction and in regard to venous sclerosis

CHANGES OPHTHALMOSCOPICALLY VISIBLE IN RETINAL VASCULAR DISEASES IN GENERAL

Localized Variations in Arterial Caliber —The phenomenon of beading of the retinal arteries was first described by Raehlmann[27]

who also studied its histological significance He described the condition as produced by a localized proliferation of the intima resulting in small mound like protrusions into the vessel lumen

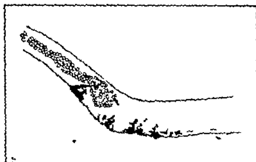


Fig 142 Atheromatous plaques in a retinal artery drawn from a case of albuminuric retinitis in which the retina was stained with Sudan III and examined without sectioning



Fig 143 —Atheroma of the central retinal artery in a case of albuminuric retinitis Section stained with Sudan III

His observations were confirmed by Coats[3] and a number of other investigators A study of the illustrations of these workers will convince anyone familiar with modern histological technique that they were describing small atheromatous plaques Such atheromata

occur commonly in the larger branches of the retinal arteries but are not found beyond the tertiary branches Beading of the smallest vessels is due to a different process an irregularly distributed hyaline degeneration of the vessel wall

Histological studies show that atheromata occur more frequently in the central retinal artery in its intraneural course than in the retinal branches Favorite sites are at the points where the vessel enters the optic nerve sheath and where it passes through the cribriform plate The presence of scattered minute atheromatous plaques in the retinal branches may be considered as the visible outposts of a process which is more developed in the central arterial stem beyond the view of the ophthalmoscope

A few writers have maintained that beading of the arteries may be due to local spasm but the usual persistence and immobility of the lesion are against this interpretation in most cases On the other hand transient localized constrictions of the arteries are not uncommon in the toxemias of pregnancy and in arteriolar sclerosis as noted above This phenomenon however is to be differentiated from the more frequent stationary beading of the vessels

General Changes of Arterial Caliber —In a variety of conditions the retinal arteries are diffusely dilated The cause may be local such as eye-strain or local inflammatory diseases or general such as congenital heart disease leukemia polycythemia fever etc Such states are functional without histological equivalents In

oles the larger retinal branches may be diffusely dilated In these cases the condition is purely functional and not associated with any morphological changes in the arterial wall The author has not seen in a retinal artery a simple hypertrophy of the media which might be considered as a functional response to long-continued hypertension

A very common finding in the early stages of albuminuric *retinitis* consists in areas of capillary hyperemia scattered throughout the retina often surrounding the cotton wool spots In these regions the capillaries not only are dilated but also present tortuous varicosities In some instances the varicosities may be seen in post mortem specimens If the foregoing theory of the relation of vascular spasm to arteriolar sclerosis is correct these areas of capillary hyperemia may represent the physiological response to anoxemia *of the adjacent tissues*

Diffuse constriction of the whole retinal arterial tree is commonly seen in the atrophic stages of local disease and in cases of arteriosclerosis *with hypertension* The clinical correlations and signifi

cance of this and other ophthalmoscopic findings in arteriosclerosis and hypertension have been discussed at length in an article by H Friedenwald and the author,[10] and will not be dealt with here [illegible]

lumen by a thickening of the arterial wall In these cases, very marked atheromatous changes in the neural portion of the central retinal vessel are found The retinal vessels presumably are narrow because the central stem behind the disk is partially obstructed and the pressure within the retinal branches reduced It has been argued that the diffuse constriction of the arterial tree in the late stages of albuminuric retinitis is unlike that commonly seen in old people, and that, while the latter may be due to atheromatous changes farther back in the arterial tree the former is due to spasm Against this interpretation is the fact that those cases show marked atheroma of the intraneural portion of the vessels and cannot be dilated by amyl nitrite or histamine as the author has repeatedly found

In many of these cases, especially in old people the retinal arteries are not only narrow but straight and branch at acute angles, giving the appearance of having been drawn into the disk It is possible that the sclerotic process in the central stem may be characterized not only by an encroachment on the lumen, but also by a shrinkage in length as Thoma[32] suspected in relation to the vessels of the limbs General reduction in the caliber of the retinal arteries is the end-stage of the process that first manifests itself in beading of the arteries, and the two conditions are often seen together As has been noted above, these cases when not complicated by local disease or cardiac decompensation or similar cause of temporary reduction in blood-pressure, invariably have hypertension It seems likely that these cases belong to the group studied by Gull and Sutton[16] and later by Bordley and Baker,[2] in which a close correlation was established between the blood-pressure level and pathological findings in the arteries of the medulla oblongata, the arteries involved being similar to the central retinal vessels in size

Arteriovenous Constriction —From the anatomical peculiarities of the arteriovenous crossings, it is obvious that a constriction of the vein at the point of the crossing may be produced in several ways 1. If the artery is displaced as a result of increased or decreased tortuosity it must drag the vein with it and if the drag is sufficient produce a constriction at the crossing This perhaps ought to be spoken of as arteriovenous displacement It occurs in conditions in which the tortuosity of the arteries has recently been increased and in the cases of shrinkage of the arterial tree

mentioned above It has been credited as a sign of hypertension though in fact it may occur without change in the blood pressure No histological changes are associated with arteriovenous displacement unless marked venous stasis is produced

2 If the arterial wall becomes thickened and its external diameter increased it must encroach upon the space within the common arteriovenous adventitia and constrict the lumen of the veins Such conditions are found in cases of retinal arteriosclerosis when in addition to atheromatous plaques of the intima a fibrous thickening of the media and adventitia is present This need not be associated with hypertension or renal disease but is due to retinal

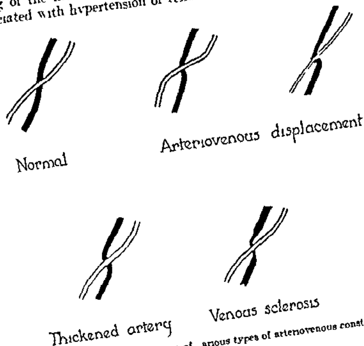


Fig 144 —Schematic illustration of various types of arteriovenous constriction

arteriosclerosis More commonly the thickening of the vessel wall is due to arteriolosclerotic thickening of the media with hyaline degeneration This is invariably associated with hypertension and sooner or later complicated by renal disease The condition can be recognized ophthalmoscopically when the vein is seen to curve sharply around the artery without necessarily being displaced laterally in its course

3 Owing to the fact that the arteriovenous wall is a single indivisible structure sclerotic changes in the artery may extend into the vein sometimes reaching up and down the vein for a short distance from the crossing This accounts for the extraordinary



Fig 145 — Arteriovenous crossing in a case of generalized arteriosclerosis Note thickened adventitia



Fig 146 — Arteriovenous crossing in a case of albuminuric retinitis Note thickened adventitia and atheromatous plaques in both vessels



Fig 147 — Fat granule cells about the veins in the regressive stage of a case of albuminuric retinitis These veins showed *intense perivascular stripes* on ophthalmoscopic examination shortly before death.

frequency of retinal venous sclerosis and thrombosis. Veins of this size in other organs show such lesions only with the greatest rarity. *Ophthalmoscopically this sclerosis of the retinal veins* can be recognized by a narrowing of the venous blood column for a short distance on either side of the crossing. This phenomenon is the result of arteriosclerosis, not of hypertension, and may occur in the absence of hypertension or renal disease. This explanation of the cause of venous sclerosis is important because of the light it sheds on the problem why the small veins in the retina so commonly suffer from sclerosis and thrombosis, while veins of similar size in other organs are hardly ever affected by these lesions.

Increased Visibility of the Vessel Walls.—The normal invisibility of the vessel walls is the result of the fact that they are optically *homogeneous structures*. *Optical inhomogeneity is produced by* fibrosis of the media or adventitia. This can be seen in the larger vessels in cases of postneuritic optic atrophy in which there is connective tissue and glial proliferation in the vessel sheath. A similar condition occurs occasionally in the advanced stages of retinal arteriosclerosis. In the smallest arterioles the hyaline degeneration of arteriolosclerosis is associated with large amounts of lipoid. When this process becomes advanced in a small vessel the wall becomes visible as a "silver wire." In the larger vessels the hyaline deg
much lipoid anc
creased but m
blood column
uric retinitis an
damage need not be due to sclerotic changes but is often the result of an infiltration of the perivascular spaces with large mononuclear wandering cells engaged in removing lipoid and other cellular debris from the injured retina.

that the appearance of copper wire and silver wire arteries represented advanced grades of retinal arteriolar sclerosis with hyaline thickening of the media. In several cases which the author was able to examine microscopically shortly after fundus drawings had been made he was able to confirm Foster Moore's findings. This change is of importance since it represents the advanced stage of the particular vascular lesion which precedes and accompanies albuminuric retinitis.

Changes in the Vascular Light Reflex.—The light streak on the retinal vessels has been elaborately discussed by Dimmer,[7] Kreiker and H. Friedenwald,[9] each of whom reached somewhat different conclusions as to the physical basis of this reflection. The more

recent studies of Wilmer and his co-workers[59] have confirmed and and extended the conclusions of H Friedenwald as follows Reflection of light can occur in transparent media only at surfaces separating media of the different refractive indices Over the

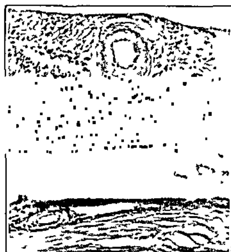


Fig 148 —Hyaline degeneration and thickening of the media of a large retinal artery in a case of albuminuric retinitis This vessel had the appearance of copper wire on ophthalmoscopic examination shortly before death



Fig 149 —Hyaline degeneration of the small arterioles in the retina in a case of albuminuric retinitis The minute vessel on the left has a lumen smaller than the diameter of a red blood cell

retinal arteries reflection can take place at the retinal surface at the boundary between adventitia and media and at the endothelial surface The reflection by the retinal surface is very brilliant and can usually be separated from that of the arterial wall by slightly tilting the ophthalmoscope mirror The adventitia has normally the same index of refraction as the surrounding retina and does not contribute to the reflex Increased width of the arterial reflex relative to the width of the blood column occurs when there is thickening of the media Increased brightness of the reflex occurs when as in hyaline degeneration of the media the index of refraction of the media is increased This is responsible for the copper wire appearance of the larger retinal vessels in retinal arteriolar sclerosis



Fig 150 Extreme hyaline degeneration of a retinal arteriole with complete occlusion of the lumen This vessel had the appearance of a silver wire on ophthalmoscopic examination shortly before death

PATHOLOGICAL CHANGES IN RETINAL VASCULAR SCLEROSIS

Summary — A consideration of the changes in the retinal blood vessels in vascular disease leads to conclusions and suggestions which may be of importance in the interpretation of vascular disease in general Naturally such conclusions based on the study of a single organ are tentative However a volume of this kind seems the appropriate place to state such tentative hypotheses which fit well the data of a single small field leaving to other contributors the decision as to whether these data fit equally well other fields in the general domain

chemically from the lipoid in atheroma, or at least is differently bound by the tissue proteins

As this process advances some capillary loops may show a similar change, as do the capillaries of the kidney glomerulus under the same conditions The larger retinal vessels also become affected Here the hyaline degeneration is limited to the media which becomes thickened In extreme cases the vessel may become completely necrotic and be represented on section by a solid structureless cord of hyaline In the larger vessels the lipoid element of the hyaline is not always demonstrable by the usual stains It may be absent or merely differently bound by the tissue proteins Secondary to this change in the media there is usually a fibrous thickening of the adventitia in the larger vessels

In the late stages of this process atheromatous changes appear in the larger vessels and proceed in their usual manner Whether these late atheromatous lesions are the result of retinal damage and atrophy or of some constitutional cause the author cannot say

Retinal arteriolar sclerosis occurs almost invariably in arteriolosclerotic nephritis likewise in cases of general arteriolar sclerosis irrespective of renal involvement It occurs commonly in severe cases of toxemia of pregnancy It also occurs in cases of chronic [illegible] been preceded and accompanied by severe hypertension

ALBUMINURIC RETINITIS

The distinction between atheromatosis and arteriolar sclerosis of the retinal vessels recommends itself on clinical and pathological grounds and is further reinforced by the fact that the ophthalmoscopic picture of albuminuric retinitis invariably is accompanied by retinal arteriolar sclerosis but does not occur in uncomplicated atheromatous disease of the retinal vessels Morphologically, albuminuric retinitis is characterized by the following features

1 Edema of the retina and optic disk
2 [illegible] ions in the retina
3 [illegible]
4 [illegible]
5 Arteriolar occlusion and retinal infarction
6 Secondary and reparative processes
   (a) Lipoid especially cholesterol deposits about the retinal lesion

(*b*) Fat droplet cells
(*c*) Scarring of the retina and glial proliferation
(*d*) Cystic degeneration

All these morphological changes may occur isolated or combined in other retinal diseases The characteristic feature of albuminuric retinitis is the combination of these changes and their anatomical distribution resulting in the production of a recognizably specific ophthalmoscopic picture

Retinal Edema —The characteristic feature of the retinal edema [illegible]

cerebrospinal fluid pressure and the edema of the optic disk may be explained as the superposition of the ordinary process of choked disk due to increased intracranial pressure upon the general picture of albuminuric retinitis

The cause of the retinal edema cannot be the decreased osmotic pressure of the plasma proteins as in the generalized edema of the nephrotic where retinal edema does not occur nor could any con stitutional cause well explain such a localized lesion as the retinal edema of albuminuric retinitis The same objection can be made against explaining the edema on the basis of changes in capillary blood pressure and capillary permeability

In searching for some local peculiarity of the macular portion of the retina to explain its susceptibility to edema in this condition one finds that the minute venules which radiate spokewise from the fovea are almost always crossed by the superior or inferior macular arteries before they reach the superior or inferior temporal veins to which they are tributaries Similar crossings of minute venules by larger retinal arteries are rarely found elsewhere in the fundus and when occurring outside the macula it is in isolated uncon nected [illegible]

istic location of the retinal edema

The albuminous fluid which escapes into the retina in part seeps into the vitreous where it cannot be recognized clinically but where it is regularly found in histological sections In severe cases some fluid escapes from the outer surface of the retina producing a flat detachment In most cases these detachments remain localized but may in some instances become complete especially in retinitis gravidarum

Within the retina the extravasated fluid tends to accumulate in certain locations for the understanding of which the detailed anatomy of the retina is needed Outside of the fovea the retinal capillary bed is divided into two systems [34] One bed of capillaries lies in the nerve fiber layer the other mainly in the inner molecular layer These capillary systems are separated by the layer of ganglion cells in which the supporting structure of the retina is especially developed Extravasations of fluid hemorrhages for instance in one of these layers usually do not cross the barrier in the region of the ganglion cells In the nerve fiber layer these extravasations tend to spread mainly along the nerve fibers Thus the flame-shaped hemorrhages occur If the extravasated fluid is rich in proteins especially fibrin we have a fuzzy grayish mass recognizable ophthalmoscopically as a cotton wool spot

In the deeper layers of the retina there are two favorite positions for the accumulation of fluid These are the inner molecular layer (the layer of bipolar cells) and the outer granular layer (the layer of fibrils connecting the nuclei of the rods and cones with the bipolar cells) In both these layers the supporting structure of the retina is feeble and the tissues are readily spread apart resulting in the formation of cyst like spaces filled with fluid Near the optic disk these spaces tend to run together forming an irregular network pattern In these spaces the fluid is usually albuminous in character and because it differs little in refractive index from the surrounding retina it is rarely visible with the ophthalmoscope Occasionally however the network pattern of these extravasations may be seen

The outer granular layer the second favorite site for the accumu

debris or when after long stan ling their protein content becomes
ver s white dots and
for
l with a fluid of
low protein content but in a progressive disease the protein content increases and they may eventually appear as hyaline or colloid masses Not all these deposits originate from local edema Some repre ent the remains of old petechial hemorrhages or of exudates of plasma fall u
minuric reti dis
turbance ar ind
hemorrhage of

the underlying lesion and in albuminuric retinitis the star shaped figure at the macula is most frequently produced

Retinal Hemorrhages —The retinal hemorrhages require little further comment Petechial hemorrhages occur in other organs as well as in the eye The exact mechanism of their occurrence is not known They are more frequent and numerous where there is venous stasis than elsewhere

Cytoid Bodies —A frequent finding in albuminuric retinitis is a localized thickening of the nerve fiber layer of the retina usually about 0 1 mm in diameter and one third to one half this in thickness In the center of these thickened areas one finds curious cell like masses called *cytoid bodies* They are globular structures some 20 to 30 μ in diameter with a sharply outlined dense eosinophilic nucleus in the center They were at first considered *pathognomonic of albuminuric retinitis but now are known to* occur in all other retinal diseases in which hemorrhages are frequent They were thought to be swollen varicose nerve fibers in cross-section but studies in serial section show that they are globular not tubular structures

Arranging a large number of these lesions in such a way as to show their stages of growth and resolution the author reached the conclusion that they represent merely one form of the organization of retinal hemorrhages and ischemic infarcts and that the cytoid bodies are large mononuclear wandering cells which accumulate in reaction to hemorrhage and are partially necrotic Verhoeff[33] has disputed this interpretation pointing out that similar bodies are found in the glioma of the optic nerve He believes that the cytoid bodies are of glial origin The question remains open

Detachment of the Retina The relation of retinal detachment to the retinal edema has already been commented on Since the detachment is commonly of small extent it is readily masked by the retinal edema and rarely recognized with the ophthalmoscope On section it is rarely found absent

Arteriolar Occlusion and Retinal Infarction —A not uncommon occurrence in the course of albuminuric retinitis is the occlusion of one or more small arterioles with resultant infarction of a portion of the retina Only the two inner layers of cells die as the result of such an injury as the outer layer gets its nutrition from the choroid Usually there is some hemorrhage at the margin of the infarct The subsequent course is as usual the debris being removed by phagocytes and the defect being healed by glial and connective tissue proliferation Occlusion of the terminal arterioles in the retina is a common feature of severe albuminuric retinitis and is responsible for many cotton wool spots Here the tissue necrosis is not very extensive and healing may take place with little loss of function During the process of healing the cytoid bodies form

42

an important part of the histological picture Vessels of this order cannot ordinarily be seen with the ophthalmoscope, but a good example of the relation of the arterial occlusion to the area of edema and necrosis is shown in Fig 151.





Fig 152 —Section of a cotton wool spot similar to that shown in Fig 151 Edema and necrosis of the tissue with surrounding hemorrhage

More rarely one sees with the *ophthalmoscope occlusions of the* smallest visible arterial branches, that is, of vessels just one order larger than the terminal arterioles All instances of this kind which the author has studied were in cases of malignant hypertension, and in all cases the duration of life following this retinal vascular accident was short—six to eight months



Fig 153 —Late stage of a cotton wool spot in a case of albuminuric retinitis showing the accumulation of cytoid bodies



Fig 154 —Serous extravasations in the retina in albuminuric retinitis

Secondary and Reparative Phenomena —The destruction of retinal tissue attributed to stasis, hemorrhage etc, brings in its wake a variety of secondary and reparative phenomena The lipoid content of the retina as of the brain is very high, and any local lesion is followed by the accumulation of lipoid débris This is taken up by large mononuclear phagocytes, which engorge the

an important part of the histological picture Vessels of this order cannot ordinarily be seen with the ophthalmoscope, but a good example of the relation of the arterial occlusion to the area of edema and necrosis is shown in Fig 151.



Fig 151 —Photomicrograph of a 'cotton wool spot' in a case of beginning albuminuric retinitis The retina was stained with Sudan III and mounted flat on a slide without sectioning The dark hazy area in the center is the 'cotton wool spot' diffusely stained as the result of beginning lipoid disintegration The arteriole supplying this area is completely obstructed by a hyaline lipoid thickening of its wall

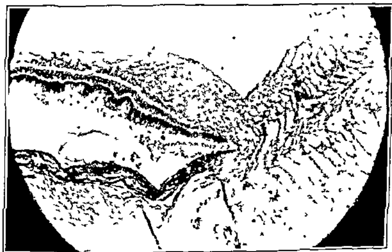


Fig 152 —Section of a 'cotton wool spot' similar to that shown in Fig 151 Edema and necrosis of the tissue with surrounding hemorrhage

and in all cases the duration of life following this retinal vascular accident was short—six to eight months

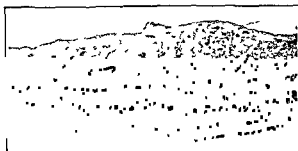


FIG 153 —Late stage of a cotton wool spot in a case of albuminuric retinitis showing the accumulation of cytoid bodies



FIG 154 —Serous extravasations in the retina in albuminuric retinitis

Secondary and Reparative Phenomena —The destruction of retinal tissue attributed to stasis, hemorrhage, etc, brings in its wake a variety of secondary and reparative phenomena The lipoid content of the retina as of the brain is very high and any local lesion is followed by the accumulation of lipoid débris This is taken up by large mononuclear phagocytes which engorge the

an important part of the histological picture Vessels of this order cannot ordinarily be seen with the ophthalmoscope, but a good example of the relation of the arterial occlusion to the area of edema and necrosis is shown in Fig 151



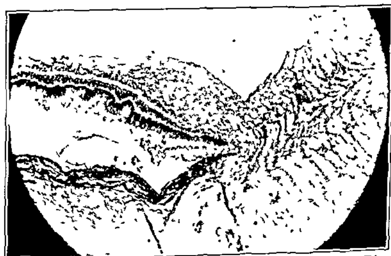


Fig 152 —Section of a 'cotton wool spot' similar to that shown in Fig 151 Edema and necrosis of the tissue with surrounding hemorrhage

More rarely one sees with the ophthalmoscope occlusions of the smallest visible arterial branches, that is, of vessels just one order larger than the terminal arterioles All instances of this kind which the author has studied were in cases of malignant hypertension, and in all cases the duration of life following this retinal vascular accident was short—six to eight months



Fig 153 —Late stage of a cotton wool spot in a case of albuminuric retinitis, showing the accumulation of cytoid bodies



Fig 154 —Serous extravasations in the retina in albuminuric retinitis

Secondary and Reparative Phenomena —The destruction of retinal tissue attributed to stasis, hemorrhage etc, brings in its wake a variety of secondary and reparative phenomena The lipoid content of the retina as of the brain is very high, and any local lesion is followed by the accumulation of lipoid débris This is taken up by large mononuclear phagocytes, which engorge the

fat and distend their protoplasm into a foamy mass filled with fat granules. During the acute stages they are found in large numbers in the retina tending to accumulate in the same loose layers as the extravasations already referred to. In later stages they migrate away from the lesion by way of the loose tissue spaces about the retinal veins and are ophthalmoscopically visible as yellowish white streaks bordering the veins.

Some of the lipoids liberated by injury, especially cholesterol, ... lize at the margin of the lesion and when present in ... lmoscopically visible either as ... conglom

t

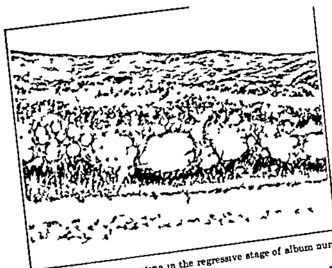


Fig 155 —Fat granule cells in retina in the regressive stage of albuminuric retinitis

Eventually the damage is repaired by connective and glial tissue proliferation. In the organization of subretinal hemorrhages the glial proliferation is marked, resulting in the snow bank masses which are sometimes seen in the late stages of albuminuric retinitis but more characteristically in retinitis circinata and other aberrant forms of retinal vascular disease. With the scarring considerable distortion of the retina may occur and the fluid spaces which are found early in the edema may become organized into definite thin-walled cysts lined by proliferated glia. The further course of these atrophic and reparative processes and of the accompanying partial atrophy of the optic nerve is not characteristic.

In the usual case the atrophic and reparative phase is not clearly separated from the stage of active lesions, fresh hemorrhages and serous extravasations being found side by side with reparative processes. Few individuals suffering with albuminuric retinitis live

long enough to allow completion of the process of repair In a few cases, collateral venous and arterial channels develop, replacing those obstructed in the course of the disease and the active process ma

I

sio

essential difference between the retinal lesions which form the picture of albuminuric retinitis in these three conditions In all three the retinal vessels show typical arteriolosclerotic changes Cases vary in the speed and malignancy with which the retinal lesions develop It is natural to expect that those cases in which the vascular disease proceeds most slowly will permit of some circulatory compensation so that the appearance of the ischemic and

On the other hand cases of toxemia of pregnancy and cases of malignant or fulminating nephritis may run their whole course in a few weeks or months In such instances there is at the outset no ophthalmoscopic evidence of disease of the retinal vessels antecedent to the retinitis Sclerosis of the terminal arterioles, however, is not wanting Such clinical distinctions as exist between the retinitis of glomerulonephritis and of pregnancy on the one hand and the retinitis of malignant hypertension on the other seem to be due to the rate of development of the process rather than to any intrinsic differences between them

Discussion —The conception of the pathology and pathogenesis of albuminuric retinitis advanced in these pages may seem unduly morphological It must then be pointed out that the morphology of the retina is extremely complicated and little known to those

morphology of the retina and its vascular system can the ophthalmoscopic picture be understood and interpreted

OTHER OCULAR LESIONS IN NEPHRITIS AND HYPERTENSION.

Aside from the retinal affections a few other ocular complications of nephritis and hypertension may be briefly mentioned

Edema of the Lids—The loose subcutaneous tissues of the lids like those of the scrotum are specially prone to edema not only in nephritis but also in local inflammatory diseases Whether this is *due to an unusually high permeability of the capillaries or to an* unusually low tissue pressure in this region is not known Early writers were puzzled over the absence of edema of the lids in cardiac decompensation in contrast to its presence in nephritis Modern *studies have removed this difficulty Nephritic edema is the result* of decreased osmotic pressure of the plasma proteins It exerts an equal force in all tissues and produces the most marked effects in those regions where fluid can most readily accumulate Cardiac *edema is the result of increased venous pressure which enables* fluid to leak out of capillaries damaged by stasis Its most marked effect is in the dependent portions No cardiac patient could live long with sufficient venous pressure and stasis in his head to cause

[illegible] a positive von [illegible] Anatomical [illegible] not revealed the cause of the exophthalmos

Lipoid Arcus—The occasional occurrence of a corneal opacity [illegible]

[illegible] branes though the stroma of the cornea is also affected The [illegible]

[illegible] mental animals by feeding a diet high in cholesterol it seems reasonable to assume that the high blood lipoid content of nephrosis is responsible for the arcus

REFERENCES

[illegible] 1909 Exophthalmos and other eye [illegible]

[illegible] rterio- [illegible] Johns

[illegible] 1 338- [illegible]

[illegible] Auges

4 CARL, A 1887 Ein Beitrag zur pathologischen [illegible] Auges bei Nierenleidenden Wiesbaden

5 COATS G 1908 Intraocular vascular disease Ophthalmoscope 4 605-621

6 Co EN M 19 ? S gnificance of pathological changes in the fundus n general arter al and kidney diseases Trans Ophth Sect Am Med Assn pp 60–79
7 Dimmer Fr 1891 D e ophthalmoscop schen Licl treflexe der Netz haut Le pz g
8 Duke Elder W S 19 6 Ocular circulation ts normal pressure

13 Fr edenwald J S and Rones B 1930 Some ocular les ons n sept cemia Trans Am Ophth oc 28 286–300
14 Gold te n I and Wexler D 19?9 The ocular patho ogy of peri arterit s nodosa Arch Ophth 2 288–?99
15 Gowers W R 1876 The state of the arteries in Bright s d sease Br t Med J 202 743 745
16 Gull, W W and Sutton H G 18 2 On the patho ogy of the

a buumu ca Al Augem u3 o 193
?3 Larsson S W 1923 Choked disk n nephrit s Acta ophth 1 193 214

33 VERHOEFF, F H Personal communication
34 [illegible]
mentel
35
haut
[illegible]

PART VI

CLINICAL ASPECTS OF BRIGHT'S DISEASE

CHAPTER XXXIX

UREMIA

By FRANZ VOLHARD, M.D.

Introduction.—The most important advance in the understand-

effects of kidney diseases on the whole organism can still be regarded as formerly as results of renal insufficiency, i. e., whether they are renal or not. The question should be asked for each symptom: Does it occur *only with* manifested renal insufficiency or *also without* renal insufficiency.

Hypertension

as in anuria

nothing to do

connected *in some way with renal circulation*

renal insufficiency has led to a revision of the old concept of uremia

Under the term *extrarenal or false uremia* we classify a variety of symptoms originating chiefly from the central nervous system that occur even when renal insufficiency is not present. Here we are

optic

ffuse

but

emic

circulatory phenomena occur in chronic primary or secondary hypertension.

ECLAMPTIC UREMIA

The clinical picture of eclamptic uremia is charcterized by signs of increased intracranial pressure, both general and localized. There are present headache, vomiting, slowing of the pulse-rate, possibly

33 VERHOEFF, F H Personal communication
34 [illegible]
mentel
35 [illegible]
haut [illegible]
Monatsbl f Augenheilk , 79, 148-158
36 VOLHARD, FR 1929 Die Pathogenese der Retinitis albuminurica, Zentralbl f d ges Ophth , 21, 129-136
37 WARBURG, O , POSENER, K , AND NEGELEIN, E 1924 Ueber Stoff-

PART VI

CLINICAL ASPECTS OF BRIGHT S DISEASE

CHAPTER XXXIX

UREMIA

By FRANZ VOLHARD M D

Introduction —The most important advance in the understanding of the problem of kidney diseases is derived from a better insight into the nature of renal insufficiency This insight has led to the important question whether the well known and severe remote effects of kidney diseases on the whole organism can still be regarded as formerly as results of renal insufficiency *i e* whether they are renal or not The question should be asked for each symptom Does it occur *only with* manifested renal insufficiency or *also without* renal insufficiency

Hypertension may be observed as a result of renal insufficiency as in anuria But in the majority of instances hypertension has nothing to do with renal insufficiency though it is a phenomenon connected in some way with renal circulation

The situation in regard to uremia is more intricate The question as to which phenomena of this variegated symptom complex occur only with renal insufficiency and which may occur also without renal insufficiency has led to a revision of the old concept of uremia on the basis of a different pathogenesis

We characterize the phenomena which occur exclusively with renal insufficiency as *true uremia*

Under the term *extrarenal or false uremia* we classify a variety of symptoms originating chiefly from the central nervous system that occur even when renal insufficiency is not present Here we are forced to recognize two separate groups The first acute eclamptic uremia is frequently encountered in acute and subchronic diffuse nephritis and still more frequently in eclampsia of pregnancy but rarely in nephrosis the second consisting of the pseudouremic circulatory phenomena occur in chronic primary or secondary hypertension

ECLAMPTIC UREMIA

The clinical picture of eclamptic uremia is charcterized by signs of increased intracranial pressure both general and localized There are present headache vomiting slowing of the pulse rate possibly

papillary edema or choked disk They might be looked upon as premonitory of the eclamptic seizure As silent premonitory signs there may be found increased knee- and ankle jerks, positive Babinski reflex and diminution of the abdominal reflexes The eclamptic seizure does not differ from an epileptic convulsion The picture might vary, reminding one of Jackson's epilepsy, especially in patients who for a long time have been lying on one side, resulting in cramps and paralysis confined to one side of the body In patients who have been lying long on their backs, amaurosis may occur as a convulsive equivalent The pale and puffy face empty of expression the drowsiness and apathy may also be considered as premonitory symptoms The stupor may change into coma without convulsions occurring Maniacal excitement and other psychic disturbances may occur as equivalents or as after-effects of the last seizure with or without restlessness and jactation

These phenomena may all occur without any impairment of kidney function and are usually absent in true uremia The whole picture is to be correlated with edema of the brain or at least with a disturbance of the circulation in the brain

At necropsy the brain is found edematous, pale and bloodless The statement that cerebral edema is sometimes absent is difficult to check [illegible] has become extremely [illegible] and false [illegible] the brain The latter can be recognized by a horizontal section through the brain *in situ* only, one then finds the brain filling the [illegible] compressed

[illegible] had been pressed down into the foramen magnum In such cases the lumbar pressure may not be elevated and lumbar puncture may endanger life Gorke and Toppich[10] reported a case in which the initial pressure of the cerebrospinal fluid was 60 cm water After a few *cubic centimeters had been drained* respiration stopped and death occurred Necropsy revealed the brain pressed down into the occipital opening

The interpretation of the eclamptic seizures being due to cerebral edema is supported by their occurrence in patients with *Quincke's* edema and normal kidneys The author has developed the conception that cerebral edema is due to ischemic injury of the brain capillaries *resulting from* arteriolar constriction He sees a support for this view in the fact that the eclamptic phenomena occur chiefly in patients with the pale form of hypertension and that a rise in arterial pressure usually precedes the eclamptic attacks Other authors *i e* Lichtwitz[13] and *Oppenheimer and* Fishberg [18] believe that the ischemia alone suffices to produce the eclamptic syndrome

The last mentioned authors use the term hypertensive encephalopathy Without denying that eclamptic phenomena might be

of the face and simultaneous eclamptic attacks or their equivalents were observed but elevation of blood pressure was absent, the fact that ingestion of water may precipitate eclamptic seizures that eclamptic seizures with practically complete success are prevented by withdrawal of salt and water that eclamptic manifestations disappear following administration of hypertonic solutions of magnesium sulphate intravenously by mouth or by rectum, all procedures which reduce the volume of the brain by withdrawing fluid from it and finally that in eclampsia gravidarum which the author considers as identical with eclamptic pseudouremia Zangemeister has demonstrated a very high intracranial pressure

The author believes that in the presence of cerebral edema the onset of the eclamptic symptoms is facilitated by the active chemical mechanism of hypertension and we may believe that in the presence of cerebral edema the high blood pressure *per se* will increase the intracranial pressure pressing the brain against the cranial wall It is however to be noted that Rowntree[21] succeeded in producing a marked increase in intracranial pressure and convulsions by continued ingestion of water alone

In regard to prevention and treatment of eclamptic pseudouremia it should be recalled that Nonnenbruch [17] in 80 patients with war nephritis observed 16 instances of eclamptic convulsions After the adoption of the hunger and thirst treatment Nonnenbruch saw only 1 instance of eclamptic uremia among several hundred cases and in this 1 case he found that the patient had secretly obtained enough fluid to increase his weight by 5 kg Similar results are reported in regard to the prevention of eclampsia of pregnancy by the same treatment

THE PSEUDOUREMIC SYMPTOMS OF CHRONIC HYPERTENSION

Symptoms in many respects similar to those encountered in acute

bulk of the symptoms we believe are correctly interpreted on the basis of ischemia or vasoconstriction and there may exist either a

frequency to headaches and vertigo there occur transitory amaurosis hemiopia aphasia astereognosis transitory monoplegia and hemiplegia and rarely epileptiform attacks

As equivalents to the cerebral symptoms peripheral symptoms occur such as numb fingers intermittent claudication angina pectoris all signs of transitory interference with the circulation Further one might have occasion to observe sudden elevation of the blood pressure with or without other symptoms conditions described by Pal a long ago under the name of vascular crises. Psychic disturbances of varying severity might develop occasionally resembling dementia paralytica Finally we enumerate the most characteristic symptoms retinitis albuminurica paroxysmal dyspnea and Cheyne-Stokes respiration

It may be accepted as certain that the transitory cerebral episodes and the psychic symptoms too are due to functional circulatory disturbances in the respective centers or areas It is not settled whether within these centers or areas arteriosclerosis of the cerebral vessels is always present or whether a localized vascular spasm as suggested by Pal might occur even where there is no local disease It is well known that we cannot predict the behavior of the arteries in hypertensive patients They may show a reversed reaction after interruption of the circulation and respond not as normal arteries with dilatation but with continued contraction Thus the angiospastic insults may become the precursors of permanent lesions thrombosis or cerebral hemorrhage (See below)

The presumption of cerebral ischemia presupposes the active mechanism of pale hypertension and it will be of interest in the future to analyze the cerebral symptoms which occur in pale hypertension only and which may be found also in red hypertension The one pathological process so far which occurs only in pale hypertension and definitely proves that in the mechanism of elevating the blood pressure we deal with a general vasoconstriction is retinitis albuminurica. This was formerly generally considered a sign of uremia The author has shown that this important extrarenal symptom occurs even with fully preserved renal function without demonstrable renal insufficiency It is not an azotemic retinitis as Widal thought Its occurrence is closely connected with an elevated blood pressure although not as many still believe directly with the pressure but rather with the vasoconstriction as the result of the hematogenous active mechanism of pale hypertension It should be named *angiospastic retinitis* rather than hypertensive retinitis The retinal changes the author considers the result of the intense arterial ischemia This concept seems important for the understanding not only of the retinal disease but of the renal change as well If the histological changes of the retina which are the result of the angiospastic ischemia are examined in detail

albuminuric retinitis most frequently and in its worst form For a detailed discussion of the histology of the retinal changes, see Chapters XXXVII and XXXVIII

Turning to the paroxysmal dyspnea occurring in hypertensive patients, two types, cardiac asthma and bulbar or cerebral asthma, must be distinguished having separate pathogenesis

It is easy to correlate *cardiac asthma* with the failing of the left ventricle, but it is difficult to explain its paroxysmal and nocturnal occurrence when the patient is at complete rest while it is absent during the hours of the day when the demands upon the patient and upon his heart seem far greater The author has observed that these attacks can be prevented with the accuracy of an experiment if no fluid intake whatsoever is allowed later than the preceding noon hour He, therefore, sees in the nocturnal paroxysms an expression of the overloading of the weakened heart by the absorption of occult edema, facilitated by the recumbent position This sudden influx of fluid is more than can be handled

might under similar circumstances promptly bring on an attack of cardiac asthma Allowing the legs to hang down or, better, tying off the limbs often used with great success, throttles the afflux from the periphery, thereby diminishing the blood supply to the right heart But these facts do not explain the inner mechanism of the paroxysmal dyspnea If the left ventricle is failing while the function of the right ventricle is unimpaired or relatively less affected, an increased pressure in the pulmonary circulation must result Thus an attack of cardiac asthma often leads to the production of pulmonary edema Possibly the dyspnea is due to the increased pressure in the bloodvessels of the lungs Some authors assume the dyspnea to be caused by an anemia of the respiratory center But insufficient oxygenation of the blood in cardiac asthma has not been demonstrated

Against the assumption of an anoxemia of the respiratory center speak the following clinical observations The attacks of dyspnea will disappear if the power of the right ventricle decreases and edema develops or the attacks will cease if the patient spends the night in sitting position, thus allowing the occult edema in the lower part of the body to increase The author, therefore, supposes that the increase of pressure in the pulmonary circulation might produce the dyspnea It is characteristic of this condition that the insufficiency of the left ventricle is transitory and that the heart recovers,

if left alone, as soon as the excess of fluid in the vascular system has been disposed of in the form of abundant nycturia. The excellent response to dry food and rigorous salt restriction may even be looked upon as characteristic of the condition.

The second form of hypertensive asthma, the cerebral or *bulbar* form, is attributed to angiospastic disturbances of the blood supply to the respiratory center. One might figuratively speak of an angina or intermittent claudication of the respiratory center. Good oxygenation and aeration of the blood with a tendency toward alkalosis have been found (Straub and Meier[26]). It is difficult clinically to differentiate between cardiac and bulbar asthma. If at all, the differentiation would be made on the consideration that simultaneous pulmonary edema speaks in favor of the cardiac type, while a tendency toward periodic respiration speaks in favor of bulbar asthma.

That periodic or Cheyne-Stokes respiration is caused by disturbance of the cerebral or bulbar circulation may be considered as certain. But the condition is surprisingly complicated and there seems to be no escape from considering two etiologically separate groups.

In the first group the periodicity may be considered as respiratory or hematogenous such as is seen following upon an apnea voluntarily produced in a normal individual (Haldane and Poulton[11]) and also occurring on high mountains. It is caused by a lack of oxygen in the respiratory center and is characterized by the fact that the hyperpnea coincides with a stage of slowed pulse and low blood-pressure, the latter often rising during the apnea. In this condition the lack of oxygen in the blood becomes effective as a respiratory stimulus before the gradual rise of carbon dioxide begins to act as such. The rise of the blood-pressure appearing toward the end of the apnea is the result of anoxemic stimulation of the vasomotor center and ceases with the beginning of respiration. In this type of periodic respiration the respiratory center is leading.

The different relationship between respiration and blood-pressure forms the basis for distinguishing between the two groups. One may venture that in the second group the vasomotor center is leading. Here the hyperpnea coincides with the stage of high blood-pressure and the pressure falls in the breathing pause. This type occurs in hypertensive patients and in cerebral hemorrhage. According to the brilliant investigations of Naunyn and Schreiber,[18] as also of Cushing,[5] if the circulation of the vasomotor center is disturbed, a rhythmic rise and fall of the blood pressure results, the pressure rising with anoxemic stimulation. With improved oxygen supply the stimulus ceases, the blood pressure drops until the deficient blood supply again acts as a stimulus of the vasomotor

center With this cycle the respiration runs parallel increasing with rising and decreasing with falling pressure A true apnea does not occur Instead the breathing pause represents a real cerebral asphyxia during which along with the lowered pressure there may also be present miosis adynamia nystagmus conjugated deviation unconsciousness even positive Babinski s reflexes (Tournay)

Normally the sensitivity of the respiratory center surpasses that of the vasomotor center and increases with decreasing arterial supply and *vice versa* Not so in this group here the presumption of a decreased irritability of the respiratory center is inevitable According to Schmidt[22] a reversal of the mode of normal reaction has taken place as the result of an advanced asphyxia of ganglion cells of the respiratory center Therefore in this type of periodic respiration the breathing ceases with decreasing blood pressure until the asphyctic stimulation of the vasomotor center along with the rising pressure again restores the blood supply of the respiratory center and thereby its excitability

An old observation by Elstein[6] is of interest In a severely diabetic patient with periodic breathing Ebstein observed the retinal arteries during the different phases of respiration During the breathing pause the arteries were like thin threads visible only within the disk With the return of the respiration they filled In the same way we have to imagine the condition of the cerebral circulation in the second group of periodic respiration

The frequency of irreparable cerebral accidents either by hemorrhage or softening among patients with chronic hypertensive conditions makes it logical to close with a consideration of the pathogenesis of cerebral hemorrhage Here older opinions are undergoing radical changes Rosenblath[20] expressed the original view contradicting former opinions that a lesion of the brain substance comes first and that a necrobiosis of the small arteries causes the hemorrhage secondarily Rosenblath speaks of an unknown agent characterized by active chemical and enzymatic powers attacking a circumscribed region of the brain This injury can have nothing to do with a general disturbance of metabolism or with renal function as Rosenblath believed but must be sought in a nutritional disturbance of a circumscribed area of the brain leading to injury and necrobiosis of cerebral tissue and liberation of substances injurious to the vessels Thus the problem of cerebral [illegible]

bance

The

blood

[illegible] angiospastic insults may precede an apoplectic stroke (2) Quite similar hemorrhages

result from an embolus or thrombosis (3) The combination with Cheyne-Stokes breathing certainly resulting from insufficient blood supply to the bulbar centers frequently is present

The author believes that an asphyxia of the ganglion cells of the brain which are extremely susceptible to a lack of oxygen is responsible for the acid decomposition products which paralyze the capillaries and cause necrosis of the small arteries In this way are caused the hemorrhages in the perivascular lymph channels or false dissecting aneurysms and the necrotizing process progressing from the outside to the inside of the arteries (Staemmler) Probably it is due to the special perivascular arrangement of the lymphatic channels in the brain that the injurious products and proteolytic ferments not only paralyze the capillaries but also injure the small arteries The author is inclined to attribute the peculiar predilection of the basal stem ganglia for hemorrhages to their extraordinary sensitiveness to lack of oxygen The fact that hemorrhages caused by carbon monoxide or cyanide poisoning have a predilection for the same regions also speaks for this conception

Against the older view that the hemorrhage results from rupturing of arteriosclerotic vessels in consequence of high blood pressure the following observations might be noted In the area surrounding the massive hemorrhage there are often multiple small hemorrhages (Rosenblath[29]) or the massive hemorrhage itself is composed of innumerable small diapedetic hemorrhages (Schwartz[23]) or besides the massive hemorrhage there are either widespread or symmetrical small hemorrhages in the stem ganglia on both sides Westphal observed that in addition to the hemorrhagic area there were areas of white softening Sometimes an apoplectic stroke follows a drop in blood pressure Apoplexy also occurs in young hypertensive patients without arteriosclerotic or other organic lesions of the arteries All facts pointing against the correctness of the older views

Summary — The eclamptic and pseudouremic phenomena may be termed acute and chronic false uremia These phenomena may occur without renal insufficiency being present They have a circulatory disturbance as a common pathogenetic factor The circulatory disturbance may be generalized or localized permanent or transitory of sudden or insidious onset

If the cardiovascular disturbance develops acutely changes in capillary permeability will predominate and a series of symptoms discussed above will develop on the basis of cerebral edema and increased intracranial pressure Hydrostatic factors even under these circumstances influence the localization of the edema (amaurosis hemiopia unilateral cramps etc)

The cerebral edema depends on increased capillary permeability

(liquor diapedesis) The circulatory disturbance is caused by increased intracranial pressure pressing the brain on the rigid skull

It appears that change in capillary permeability might occur without the factor of cerebral vasoconstriction (eclamptic uremia in nephrosis)

If the cardiovascular disturbance develops gradually or to an extreme degree cerebral vasoconstriction will predominate The variety of symptoms which may be interpreted as due to cerebral ischemia has been considered The symptoms are not dependent on increased intracranial pressure but on vasoconstriction and may be brought about through general increase in vasotonus without arteriosclerosis as well as through localized arteriosclerosis without generalized vasoconstriction

In the course of chronic hypertensive disease the two kinds of circulatory disturbance may merge An increase in the amount and pressure of the cerebrospinal fluid may be present

Some of the symptoms of false uremia are of purely cardiac origin (cardiac asthma)

The cerebral circulatory disturbances may be augmented through water retention due to glomerular insufficiency

A further connection between the eclamptic and angiospastic phenomena and renal function cannot be altogether neglected The appearance of angiospastic phenomena including convulsions seems to be favored through renal insufficiency Even so this does not necessitate the assumption of a retention of vasoactive substances rather of an increased production of such substances as has already been discussed in connection with pale hypertonia

TRUE UREMIA

When we compare the symptoms which appear only with renal insufficiency and which we have designated as symptoms of true uremia with those that occur in anuria we find them almost identical

The essential symptoms are as follows (1) General mental and bodily fatigue weakness drowsiness and a dulness which Widal designated as veritable narcosis (2) Excitation phenomena muscular contractions tendon jumping an increase in the skin reflexes narrowing of the pupils and deep breathing (3) Rapid loss in weight and decrease in muscle mass (4) Dyspeptic symptoms loss of appetite hiccoughs vomiting (5) Tendency to inflammation and necrosis laryngitis pharyngitis stomatitis gastritis enteritis necrotic ulcers of the mouth stomach intestinal mucosa and the skin and in addition pericarditis (6) Drop in temperature

(7) Odor of urine from the breath (8) Absence of convulsions and of headaches

The picture is always the same but not always equally complete Some cases begin with an eruption like measles or scarlet fever which directs the attention away from the kidney There are cases in which the dyspeptic symptoms are in the background and others where the diagnosis of uremia is missed because the dyspeptic symptoms dominate In some cases the muscle contractions never occur In other cases deep breathing predominates Asthenia seems to be the most constant symptom

Uremia and Retention of Waste Products —In true uremia there is isosthenuria without polyuria and a retention of urinary solids in the blood The problem of the pathogenesis of true uremia lies in the correlation of the clinical symptoms and the lethal outcome with the retention of waste products in the blood It once seemed attractive to explain the symptoms on the basis of the toxicity of the urine The experiments of Brucke[50] and of the author s co workers *Hartwich and Hessel*[54,55,56] *have shown that when the* urine from one kidney flows directly into the blood through a uretero-venous fistula the animals die sooner despite the normally functioning second kidney than after bilateral nephrectomy If the situation is complicated by previously producing a hydronephrosis of the kidney which is to be anastomosed to the vein jaundice and acidosis appear The blood shows a marked increase in non protein nitrogen and a strong xanthoproteic reaction and the animals die despite the fact that the other kidney is normal These results are difficult to interpret but it is safe to state that the animals do not die from an ordinary uremia The so-called toxicity of the urine has been much discussed and the urinary colloids have particularly been indited Pribram suspected them to be highly toxic This is not borne out by experiments by Hartwich and Kerger[57] who observed the effect upon the isolated frog s heart of urines and of artificial solutions of the same salt composition as the urines They found no evidence of any toxic effect of the urinary colloids but regularly found the artificial solutions more harmful and are inclined to attribute most of the effects to the altered potassium calcium ratio Nevertheless the old conception that the patient in uremia is urinating into his own blood cannot be maintained

Urea was the first substance to be looked upon as the cause of uremia and there are series of investigations both for and against this conception The author concludes that urea might cause the death of animals and that it might become more toxic with decreas-

blood The urea concentration in the blood in renal insufficiency can be increased by giving urea without producing uremic symptoms and true uremic symptoms may develop without any change [illegible] of the blood On the other hand decomposition of urea by bacteria will take place wherever tissues rich with urea come in contact with air or with the ubiquitous urea splitting bacteria Thus necrotic ulcers may develop on the mucous membranes of the gastro-intestinal tract and in purulent pyelonephritis ammoniacal necrosis of the kidney may be found

TABLE 84 —COMPARISON OF THE CHLORIDE AND NON PROTEIN NITROGEN CONTENT OF BRAIN AND BLOOD IN NORMAL AND UREMIC ANIMALS
(AFTER KERPEL-FRONIUS AND LEÖVEY [5])

	Gray substance		White substance		Blood		Mean duration hrs
	Cl	N P N	Cl	N P N	Cl	N P N	
Mean values for normal	173	163	166	156	345	36	
Mean values following ureteral obstruction	02	395	187	30?	302–365	203 206	67 5
Percentage change	+17	+147	+13	+94	−4	+646	
Mean values following ureteral obstruction and 10 gm urea	195	451	164	364		388	41 0
Percentage change	+5	+176	1	+133		+1080	
Mean values following ureteral obstruction 4 gm NaCl per kilo	422	191	259	165	670	73	27 7
Percentage change	+144	+17	+56	+6	+85	+103	
Mean values following ureteral obstruction 7 gm NaCl per kilo	445	1 0	318	158	657	25	9 5
Percentage change	+157	+4	+91	+1	+91		

Von Koranyi and Lindemann correlated uremia with changes in the osmotic pressure of the blood emphasizing that its molecular concentration might be increased so as to depress the freezing point to as low as −0 9° C (Straub[83]) Munzer in this saw a general salt effect but the increase in osmotic pressure is almost entirely *due to retention of the easily diffusible urea* It is conceivable that when the sum of the dissolved molecules reaches a certain height injury may be produced in the ganglion cells of the brain Blum and his co-workers[47 48 49] have compared the chloride content

of different organs including the gray and white brain matter in normals in uremia with and without nitrogen retention and in diabetic coma. In these pathological conditions they found an increase of the chlorides of the gray matter, which increase far surpassed the increases in the other organs. Kerpel Fronius and Leovey[58] found that the length of life of rabbits which had been made uremic was shortened by sodium chloride and urea feeding. The accumulation of non protein nitrogen and chlorides was found significantly higher in the gray matter of the brain than in the white. This difference correlates with the higher water content of the gray substance. Table 84 shows the mean values and percentage increase of chlorides and non protein nitrogen for the blood the white and gray matter correlated with duration of experiment. It appears that death occurs independently of duration as soon as the chloride and non protein nitrogen content of the gray matter has reached a value about 150 per cent above normal. Chabanier and Castro-Galhardo[51] see the essential sign of uremic intoxication in the increase in the non protein nitrogen exclusive of urea the residual nitrogen which shows a rapid rise during the final stage when uremic symptoms develop. It may be assumed that creatinine and perhaps also uric acid are not toxic.

TABLE 85.—CHIEF CONSTITUENTS OF PLASMA NON PROTEIN NITROGEN IN HEALTH AND RENAL INSUFFICIENCY (MG PER 100 CC) (AFTER BERGLUND[46])

	Amino acid N	Urea N	Creatinine	Uric acid	Residual N	N P N
Twelve normal young men						
Minimum	4.3	9.6			1.8	18.0
Maximum	6.2	17.3			11.5	30.0
Average	5.3	12.4			6.7	24.7
Renal insufficiency 7 instances						
1	4.3	13.0	1.8	3.7	20.0	39.0
2	5.8	47.0	2.3	6.4	18.0	74.0
3	3.5	52.0	3.0	6.1	18.0	77.0
4	5.4	71.0	8.1	6.8	21.0	103.0
5	6.2	109.0	8.1	9.3	23.0	144.0
6	7.6	214.0	14.5	18.4	52.0	295.0
7	7.3	234.0	19.2	21.0	51.0	306.0

Representative examples of the concentration of the most commonly determined constituents of the non protein nitrogen in normals and during different stages of retention up to uremia are given in Table 85. A comparison between the concentrations of the same compounds in plasma and cerebrospinal fluid is given in Table 86. It will be observed that the residual nitrogen does not pass into the cerebrospinal fluid. Looking upon the nitrogen reten

tion from the viewpoint of increased molecular concentration we remember that the urea nitrogen represents a urea concentration of a little more than double the nitrogen and that the urea concen- [illegible]

much as the urea nitrogen To this has to be added a further retention of nitrogen-free protein derivatives which will be considered later The molecular concentration of these compounds is not known

TABLE 86 —NON PROTEIN NITROGEN DISTRIBUTION BETWEEN PLASMA AND CEREBROSPINAL FLUID (MG PER 100 CC) (AFTER BERGLUND [45])

Condition	Amino-acid N		Urea N		Creatinine		Uric acid		Residual N		N P N	
	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid	Plasma	Cerebrospinal fluid
Non nephritic		2 0		11		0 9		0 8		3		17
Uremia (Case 6 Table 83)	7 5	2 8	214	218	14 5	6 1	18 4	4 5	52	0	285	222
Uremia (Case 7 Table 83)	6 7	2 6			22 0	6 3	22 6	2 6			324	238
Same 24 hrs later	7 1	3 0		272	21 3	8 5	20 6	2 6		0	348	279

In uremia the products of protein putrefaction in the intestines are increased in the blood Obermayer and Popper noticed the odor of the serum in uremia and the author has observed fecal odor from the distillate of uremic blood The serum odor might be [illegible]

test, originally making use of a strong ammoniacal reaction for the development of the characteristic color, through the work of Pauly[79] and others now may be interpreted [illegible]

reported by Becher[…] on uremic sera concern themselves with this reaction (2) In the second diazo reaction in use, known by Ehrlich but commonly connected with the name of Hijmans Van

den Bergh, the color develops in strongly acid solution This reaction seems to be specific for bilirubin (3) The third reaction* is the one related to uremic conditions It was described by Andrewes[61] as a two-phase reaction, the first phenomenon being the development of a brown buff color which on careful alkalinization passes through a characteristic pink or cherry-colored stage Harrison and Bromfield[66] have made it almost certain that the reaction is due to indican or possibly in part to indoxyl glycuronate Chrometzka[63] independently described the first step of the reaction Though the reaction has been found positive in uremic sera only, and runs roughly parallel with the accumulation of urea, it does not give the same information as to impending danger as the reaction to be discussed presently Indican does not pass into the cerebro-

* *The Diazo Test for Renal Insufficiency (Simplified Method)* —Reagents (identical with those used in Van den Bergh s test)

Solution A

Sulphanilic acid		1 gm
Concentrated hydrochloric acid		15 cc
Distilled water	to	1000 cc

Solution B

Sodium nitrite		0 5 gm
Distilled water	to	100 cc

The diazo reagent is prepared by mixing 25 cc of Solution A with 0 75 cc of Solution B The mixture may be kept for at least a week at room temperature without loss of sensitivity so far as Andrewes reaction is concerned although of course the Solutions A and B must be mixed freshly for use in the Van den Bergh test The mixture often turns slightly yellow after keeping for a day or two but this does not matter in Andrewes test

Serum or oxalated plasma is obtained from the patient in the usual way To 1 volume of serum 2 volumes of alcohol absolute or 96 per cent are added The precipitated proteins are separated by centrifuging or filtering A slightly improved extraction may be obtained by heating the mixture of serum and alcohol to the boiling point To 4 volumes of the filtrate 1 volume of the diazo reagent is added The mixture is boiled thoroughly for one half to one minute and a solution of 20 per cent sodium carbonate is added drop by drop shaking after each addition The alkali may be added immediately after the boiling

On boiling the mixture of protein free filtrate and diazo reagent a yellow brown or buff color always results in positive cases but a similar color may also be obtained in negative cases The color change on alkalinization is the essential part of the reaction The test should be called positive only when a definite pink or cherry red color is seen This pink color is fleeting It may last for a few seconds only and the mixture must therefore be observed carefully while adding the sodium carbonate In a very few severe cases of uremia the pink color may persist for longer periods even up to one-half hour The volumes recommended may be judged sufficiently well by eye without greatly lessening the sensitivity of the reaction

Substances other than that responsible for Andrewes reaction may give a yellow brown color at the first stage (in acid solution) but these other substances do not yield a red color on alkalinization (Harrison G A and Hewett L F Brit Med J p 1139 1927

The Xanthoproteic Reaction on Blood and Other Body Fluids —A 1 to 1 protein free filtrate with 20 per cent trichloracetic acid is prepared To 2 cc filtrate is added 0 5 cc concentrated HNO_3 the solution is heated one half minute cooled and 1 5 cc of 33 per cent NaOH is added A yellowish brown to reddish brown color indicates a positive reaction (Becher E München med Wchnschr No 46 1924)

spinal fluid There are reasons to look upon indican and its mother substances indol and indoxyl as relatively non toxic

TABLE 87 —CORRELATION OF UREMIC SYMPTOMS WITH XANTHOPROTEIC REACTION AND UREA CONTENT OF THE BLOOD (BECHER AND KOCH[43])

	N P N	Urea	Indican	Xanthoproteic	Uric acid	Remarks
Feb 16	124	213	+++	82	7 8	Definite uremic symptoms
20	138	224	++++	140	7 6	Vomiting muscular contractions
21		234	++++	130		Condition getting worse
25		195	++++	112	8 9	Disappearance of uremic symptoms
Mar 4	120	207		72		Condition becoming better
9	110	193	+++	60		Daily 50 gm of urea.
12	129	233	++++	42		Subjectively feels well
16		421	+++	46		No uremic symptoms
April 14	132	232	++++	80		Symptoms of true uremia

The author believes a different situation to prevail in regard to the phenol derivatives In his experience no blood test gives a better basis for prognosis in renal insufficiency than Becher s xanthoproteic reaction which informs us as to the degree of retention of aromatic substances in general Table 87 gives a characteristic example taken from the publication of Becher and Koch[43] In this case the symptoms and signs of uremia increased up to February 20 and death was expected At a urea value of 224 mg per 100 cc the xanthoproteic value reached its highest point of 140 Contrary to expectation improvement took place and with di appearance of uremic symptoms the xanthoproteic value fell to one-half whereas the blood urea remained the same From March 9 urea was given until the blood urea reached 420 mg The xanthoproteic reaction fell to 42 and to 46 scale divisions and the [illegible]

toms of uremia recurred although the urea had dropped from 420 to 232 This case proves that the uremic symptoms do not parallel the retention of urea but rather the aromatic substances in the blood Symptoms of uremia develop at colorimetric xanthoproteic values of 100 (normal up to 25 in Becher s technique)

pu
l lo
pla
rabbits they survived the operation ten hours The animals produced a water-clear urine free from phenols in lican and urochro mo-

gen and following extirpation of the kidneys no indican was found in the blood The author has observed among the large number of nephropathies in his clinic in Halle and Frankfurt not a single instance of true uremia without elevated phenol values or a strong qualitative xanthoproteic reaction Becher s findings of phenols in the blood in severe renal insufficiency and uremia is of pathogenetic significance Whenever it was possible through dietetic and charcoal treatment to free the blood of phenols improvement occurred and uremic symptoms disappeared Becher points out that the symptoms of uremia—fatigue insomnia loss of weight gastro intestinal symptoms vomiting drop in temperature, skin symptoms cachexia—remind one of the symptoms seen when the carbolic acid spray was used by surgeons and of the symptoms found among workmen in carbolic acid factories Perhaps the final decrease in kidney function might be explained by injuries due to phenols Like Becher the author is not prepared to regard uremia as a simple phenol intoxication

Though the practical value of the xanthoproteic reaction is well established the present shortcomings of the test shall not be left out of consideration Being chiefly a qualitative test the estimation of the strength of the reaction is only roughly quantitative which indeed is natural as long as the compound or compound responsible for the reaction remain unknown Since all aromatic substances react positively the identification is not easy Becher so far has found that the substances responsible for the reaction are thermostable and that there is no significant increase in color after hydrolysis that the substances are partly volatile and partly ether soluble From this Becher assumes the following compounds to participate in the reaction phenols mostly conjugated dihydroxy phenols and oxyacids The oxyacid fraction (the portion of reacting bodies extractable by ether) in 1 instance showed an increase of forty times the normal (Becher Doenecke and Litzner[4])

To what extent these compounds or others that might participate in the reaction are of intestinal origin or products of intermediary metabolism cannot be judged at present Neither is any definite knowledge possessed as to their respective toxicity Becher however made the important observation that in true uremia a part of the phenol bodies is in a free and therefore non-detoxified state in the blood They are much more highly toxic than the bound phenols The appearance of these undetoxified products of intestinal decomposition depends upon the fact that the processes are no longer ...

(Beck...

tiss ...

inte ...

Bec ... products a still further ... ance of the ... may be noted In contrast to the behavior of urea these

decomposition products do not ordinarily diffuse into the cerebro spinal fluid Their first appearance in the cerebrospinal fluid coincides with the onset of the uremic symptoms and indicates that their penetration to the central nervous system is the vital factor in the production of true uremia

of
sul
retained in the blood and in the skin They probably have not the toxic effects assumed by Thudichum The chromogens retained in the skin may go over to the colored compounds themselves by the action of light and the water-clear serum and the colorless urine

of the uremic picture to the retention of products of intestinal putrefaction So far the xanthoproteic reaction which perhaps chiefly depends upon retention of such products is the only chemical reaction of the blood which runs parallel with the degree of uremic intoxication It should not be forgotten that the classical experiments of Magnus Alsleben have shown that the intestines represent the greatest source of toxins in the organism

Uremia and Acid Intoxication? (Straub and Schlayer)—It is well known that acidosis in renal insufficiency may reach a degree incompatible with life but even if less developed it is an obligatory symptom in true uremia The severity of the acidosis sometimes

is present for several days before coma develops

Different possibilities have been considered for the cause of

(3) Abnormal production or retention of organic acids After complete analysis of the altera

questions formulated except possibly to rule out the role of decreased ammonia formation If the acidosis were founded up on a dis

turbed formation of ammonia all nephritics would remain free of uremic acidosis on a basic diet It is also not possible to explain the renewed development of acidosis after administration of large amounts of alkali on the basis of deficient ammonia formation

by
an

requisites for a solution accurate methods for the needed analyses and an understanding of the mechanism of the normal acid base balance are now on hand To facilitate the discussion the reader s attention is called to the normal acid and base composition of the plasma as given in Fig 156 With the help of the figure the acidosis in severe renal insufficiency and coma might be discussed A great number of workers have contributed to *our knowledge in this field* The data of Palmer and his co workers Peters and his staff [79 80] and Henderson[74 75] *and his group will particularly be considered*

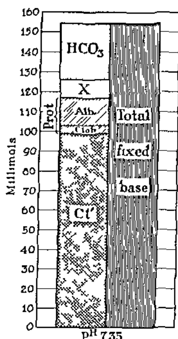


Fig 156 —Acid base composition of normal plasma

With the commonly used definition of acidosis bicarbonate deficiency is nearly always found The plasma CO_2 normally present in an amount to combine with approximately 20 per cent of the total base may become reduced by four fifths of its normal value

The chlorides normally present in amounts equivalent to approximately 66 per cent of the total base may be either increased or *decreased* which latter condition is the more commonly observed and almost the rule in extreme acidosis The negative variations may reach values 20 to 30 *per cent below the normal and are often* of greater magnitude than the positive ones The decrease is independent of the presence of edema and is the first example of

to characterize as

low chloride level

greater than would

reduced and never increased—the plasma proteins Normally the plasma proteins have been calculated probably with high degree

r cent of the total

than three fourths

With the reduc-

urs (see Chapter

XXX) the base binding capacity will diminish Peters has calculated that reductions of 50 per cent and more may be found As the acidosis reaches a degree sufficient to shift the pH toward 7, a further reduction of the proteins acid role in the plasma takes place

The three acid components of the plasma just discussed normally are equivalent to about 95 per cent of the total base So far in nephritic acidosis they have all been found decreased in numerous instances at least The cause of the acidosis thus might be found either in an increase of acid radicals not yet considered or in a decrease in the fixed base

The convenient and accurate determination of the total fixed base has made it unnecessary longer to rely upon the summation of the separate bases in which the determination of the biggest factor the sodium was uncertain at its best The total base concentration is one of the least variable among physiological constants (154 millimols) and normally is chiefly responsible for the constancy of the osmotic pressure In nephritic acidosis any type of variation in total base may occur it is seldom increased but often decreased to as low as 130 millimols or lower With such reductions there would normally be a lowered osmotic pressure but even taking into account the intricacies of cryoscopy when applied to blood serum it might be accepted as established that the osmotic pressure in nephritic acidosis may be normal or increased because of retention of non-electrolytes particularly urea which may reach a level of 50 to 70 millimols or more (100 mg urea nitrogen being equivalent to 35 8 millimols)

There is no satisfactory explanation for the base diminution If attracted by teleological viewpoints it might be inquired whether

relation with the coexistence of edema such an assumption would

necessitate another one, the so-called dry retention of electrolytes. Though invitations to accept such a concept by no means have been wanting, particularly from French clinicians its existence has never been indisputably proven. Another explanation might be sought

[illegible]

ized in the kidney and, as a matter of fact, cannot possibly be localized in the kidney alone, considering what is known about the function of the intestines in this respect. That the kidney plays an important rôle in base preservation cannot be doubted, particularly in light of the new concept of ammonia formation introduced by Nash and Benedict. Thus, as a tentative explanation of the characteristic cation deficit in severe renal insufficiency, there

[illegible]

others than the ones already dealt with. In balancing acid and base equivalents normally there is but a small acid fraction left, X obtainable by difference only. The experimental errors affecting

[illegible]

acidosis though both are said to be elevated in severe renal insufficiency. The remainder represents undetermined organic acids. In nephritic acidosis X is usually increased, frequently doubled and not very seldom tripled with values calculated as 30 to 50 millimols, as high as in diabetic coma.

With a twentyfold increase of non protein nitrogen including 50 mg residual nitrogen representing unknown metabolites with strongly positive xanthoproteic and diazo reactions, indicating retention of aromatic substances, with undetermined acids in amounts corresponding to 50 millimols, with the osmotic pressure raised by one-third and the concentration of hydrogen ions increased nearly three times, with the patient comatose, laboring with Kussmaul's breathing, a stage has been reached where all physiological regulations are on the verge of complete breakdown.

To select from this picture the symptoms which are of renal origin and those which are not is impossible. That the renal path-

* MacNider * in animal experiments studied both functionally and histologically [illegible] from excess acid and alkali. As is the case in diabetic coma, so [illegible] id material [illegible] dogs with [illegible] ficial effects [illegible] hology the [illegible] ffects upon

ology plays the most important rôle is clear, but, to quote Henderson[74] "It is manifestly impossible to regard the changes in the blood as direct effects of the pathological state of the kidney On the contrary, nothing could be clearer than that a disturbance of the whole organism exists This involves adjustments and readjustments between all the parts and at this stage the breaking-point has been reached There can be little doubt, for instance, that the blood must exert harmful action on the kidney, which is hardly less than that exerted by the kidney on the blood A similar statement will hold good for the heart and the other organs"

A problem as important as it is difficult is the identification of

of an aliphatic acidosis With his co-workers the author has found the aliphatic ketone bodies missing in uremia, neither have we found increased amounts of lactic acid In line with Becher's work we are inclined to look upon X as partly made up of aromatic oxyacids, we are as a matter of fact, speaking of an aromatic acidosis of nephritis in contradistinction to the aliphatic acidosis of diabetes

More recent investigations of Becher, Enger and Herrmann[84] have demonstrated that the acids which are present in the blood in true uremia belong to the group of organic ether soluble acids Becher and his co-workers showed by direct isolation and quantitative determination of the ether soluble fraction that, estimated indirectly, these acids are sufficient to account for the anion deficiency The acids are partly of aliphatic, partly of aromatic nature Part of them are volatile with steam distillation part of them not The author hopes to be able further to build out this structure with evidence not only of an intestinal origin as already considered but of a metabolic origin of these acid products of protein katabolism The old, once almost discarded idea about toxic protein decomposition may once more find itself reinstated on the strength of new experimental evidence

REFERENCES

General and the Pseudouremias

5 CUSHING, H 1902 Some experimental and clinical observations con-
cern ... –400
...abeti-
...klin
7 EPPINGER, H, v PAPP, L, AND SCHWARZ, H 1924 Astma cardiale, Berlin, Julius Springer
8 EYSTER, J A E 1906 Clinical and experimental observations upon Cheyne-Stokes respiration, J Exp Med, 8, 565–613
9 GESSELL, R 1925 The chemical regulation of respiration, Physiol Rev, 5, 551–595
10 GORKE, H, AND TOPPICH, G 1921 Zur Klinik und Pathologie der Sublimatnephrose, Ztschr f klin Med, 92, 113–123
11 HALDANE, J S, AND POULTON, E P 1908 The effects of want of
14 MEANS, J H 1924 Dyspnea, Medicine, 3 309–416
Rev, 2, 116–169
22 SCHMIDT, C F 1928 The influence of cerebral blood flow on respiration, Am J Physiol, 84, 202–222
23 SCHWARTZ, PH 1926 Studien zur Morphologie und Genese der ... Putamen Claustrum ...
(Bright sche Krankheit), Handb d inn Med, von Mohr and Staehelin, vol 4
, No 5
erhandl d
...atsschr. f
...a, Zentralbl
f d ges Ophth, 21, 129–130
34 ——— 1931 Die doppelseitigen hamatogenen Nierenkrankungen, Handb d inn Med, von Mohr and Staehelin, 2d ed, 6, 1–1815, Berlin, Julius Springer

True Uremia

38 BECHER, E 1924 Ueber das Vorkommen von aromatischen Oxy-

96, 642

... Beitrag zur Frage der nephro-

... und Kochsalzspiegel bei den

... Uramie, Klin Wchnschr,

56 ———— 1928 Experimentelle Untersuchungen zur Frage der Harnvergiftung, Ztschr f d ges exp Med, 59 633–655

... Analyse der

... grund der

... ges exp

... Dauer der

... Path u

59 Leövey, F, and Kerpel-Fronius, E 1929 Die experimentelle Uramie und Chlorgehalt der Kortex, Arch exp Path u Pharm, 138, 372-378
60 Lindemann, W 1914 Zur Lehre von den Funktionen der Niere, Ergebn d Physiol, 14, 618-656

Indican and Diazo Reactions

61 Andrewes, C H 1924 An unexplained diazo color reaction in

Ztschr f physiol Chem,
71 Rosenberg, M 1916 Ueber Indikanämie und Hyperindikanämie bei Nierenkranken und Nierengesunden, München med Wchnschr, 63, 117-120

Acidosis

75 Henderson, L J, Bock, A V, Dill, D B, Hurxthal, L M, and
system VI The
in terminal chronic

the influence of a
renal function and

nephritis, Physiol
Rev, 4 595-638
78 Means, J H, Bock, A V, and Woodwell, M N 1921 Studies of

Press.
chemischen Atmungs-
extensive bibliography
1932 Die ätherlöslichen
Klin Wchnschr, 11, 891-893

CHAPTER XL

TREATMENT OF ACUTE DIFFUSE GLOMERULO-NEPHRITIS.

By FRANZ VOLHARD, M D

Introduction —The Problems Involved in the Treatment of Acute Glomerulonephritis — To the practising physician one of his most important tasks is the treatment of acute diffuse glomerulonephritis It imposes a great responsibility but may also bring the greatest satisfaction

[illegible]

irreparable organic changes in the kidney *i e*, in the glomeruli or the renal arteries or arterioles, for these organic changes in glom-

[illegible]

For the understanding of the dangers it is important to bear in mind that the true process consists in a general and also a renal vasoconstriction Thus in the acute stages we are dealing with a functional condition which endangers not only the kidney but also the other organs, especially the central nervous system, and greatly threatens the heart In the acute stage it is the danger to the heart which is of first and highest importance The danger to the brain is second and to the kidneys only third The danger that the functional condition in the kidneys will lead to lasting and irreparable changes increases with the degree and duration of the general vasoconstriction manifesting itself by hypertension The hypertension, caused by spastic narrowing of the small peripheral arteries may set in suddenly, even over night. This means an enormous overload for the heart The increased work can be accomplished only if the muscle fibers of the heart are stretched more than under normal conditions (Fick and Frank s law) The distention occurs automatically through an increase of the residual blood in the heart chambers due to the overload A certain degree of dilatation of the heart thus is a necessary condition for increased work but includes a danger of overdistention

The clinical picture of acute diffuse glomerulonephritis, therefore, may present itself in the form of an acute and most severe insufficiency of the heart with dyspnea of the highest degree, increase of the venous pressure and swelling of the liver Almost every case that dies in the acute stage of the disease dies of cardiac insufficiency through overdilatation This is very clearly recognized at necropsy It is the danger which has to be avoided by all possible means For this reason it is important (1) to keep the patients strictly in bed and (2) to relieve the overtension of the cardiovascular system In critical instances the latter is accomplished by venesection but if time permits, complete restriction of fluid intake will suffice The effect of such simple procedures is often astonishing In a single day the clinical picture may change completely, and dyspnea may disappear One must not be misled by a full and regular pulse It is important to realize that a slow pulse belongs to the picture of acute diffuse glomerulonephritis A rate of 80 is too high and a sign of imminent danger Prompt use of heart stimulants is indicated as soon as the pulse goes beyond 50 to 60 Digitalis should be given in every such case The promptest result is obtained from intravenous injection of strophanthin in doses of 0 3 mg, given once or twice a day in the beginning until the pulse rate comes down

The second grave danger consists of cerebral edema, causing the convulsions of the so called eclamptic uremia This picture of so-called eclampsia, *i e* convulsive uremia, has nothing to do with the true uremia caused by renal insufficiency Convulsive uremia consists of increased intracranial pressure and the equivalent utterances of it are headache vomiting, apathy, somnolence, amaurosis (See also Chapter XXXIX) The higher the blood pressure, the greater t [illegible] by energetic [illegible] The relief of [illegible] ing with castor oil or magn [illegible] doses or by intravenous injectior [illegible] according to Blackfan [illegible] magnesium sulphate

The third danger is that of urine intoxication which threatens in acute stages only in cases of anuria or very marked oliguria In such instances surprising results have at times been seen with prompt recovery after decapsulation of the kidneys The author has observed such cases though in other instances there has been no improvement Roentgen ray treatment is reported as having given good results in some cases so has splanchnic anesthesia The secret of the results seems to lie in an improvement of renal circulation, as shown by Hulse and Litzner in animal experiments In

severe cases with anuria persisting over several days denervation

e power of
Usually
diuresis sets in with the relief of the circulatory overtension through venesection or absolute restriction of fluid intake and is favored by diathermy of the kidney region twice daily

The prevention of danger to the heart brain and kidneys in the acute stages are best affected by complete abstinence from food and drink—the so-called hunger and thirst treatment The author allows the patients to lie hungry and thirsty for three four or more days by all means until diuresis and fall in blood pressure and weight are noticed The edema as a rule disappears promptly the more promptly the earlier the patient comes under treatment The dyspnea and with it the danger to the heart diminishes the pulse slows down the body weight decreases and the edema may disappear even if the urinary volume does not increase As to the technique of the hunger and thirst treatment it should be mentioned that first of all the bowels should be thoroughly emptied In children and weakened patients the starvation treatment might be made milder and acidosis prevented by offering fresh fruit cracker potato or sugar water in small amounts or by intravenous injection of hypertonic glucose solution

The second part of the author s treatment consists in what he calls *Wasserstoss* or the dilution test In case the blood pressure has somewhat decreased and the urinary volume increased after the period of hunger and thirst he makes the water test with 3 pints (1500 cc) of weak tea early in the morning to be taken in the course of one-half or three-quarters of an hour Very often this leads promptly to a surprising diuresis a draining off of edema and a distinct decrease of the blood pressure One cannot escape the impression that the sudden flooding by the water intake favors the restoration of renal circulation and accelerates the recovery It is noteworthy that the same amount of fluid taken in divided doses during the course of the day has not nearly the beneficial effect of this large single dose which is able to produce a marked outflow of urine In case the water test is ineffective it may be repeated after two or three days during which time the patient receives a salt free diet without fluids A diuretic such as theophyllin is given with the second water intake The Wasserstoss is repeated until the blood pressure returns to normal

Criteria of Recovery The result of the treatment is judged by

atment
Part
2) the
measuring of the blood pressure twice a day

Recovery from diffuse acute nephritis should be spoken of only when the blood pressure has permanently come down to normal levels or lower

Importance of Early Treatment —For the success of the treatment the most important factor is that of time Every day that a patient walks about without having his condition recognized renders the prognosis darker and diminishes the chances of complete ultimate recovery All of our adult patients who have come to the clinic in the first weeks of the disease have completely recovered For this reason a prompt recognition of the condition, the early diagnosis of the acute diffuse glomerulonephritis, is of prime and foremost importance Not every case of nephritis starts with the clinical symptoms of acute cardiac insufficiency and dyspnea There are cases of slow development wherein the patient complains only of fatigue or headache or loss of appetite or even of nothing at all It is therefore necessary to watch for nephritis after acute tonsillitis and other infections just as we are accustomed to do after scarlet fever And we have to watch for it not so much in the acute stage of these infections as during the first two weeks following the fever

CHAPTER XLI

CEREBRAL SYMPTOMS IN ACUTE GLOMERULAR NEPHRITIS AND THEIR TREATMENT

By KENNETH D BLACKFAN MD

AND

ALLAN M BUTLER MD

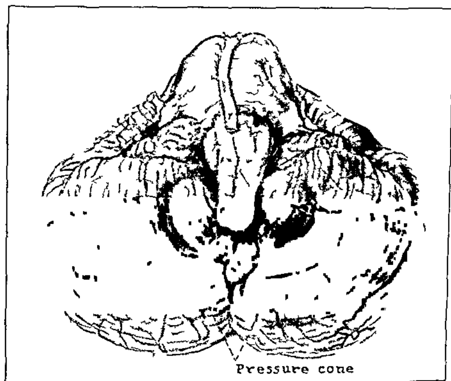
Introduction —Recent clinical classifications of Bright s disease by Addis[1] Van Slyke[10] Aldrich[2] and Blackfan and McKhann[4] are generally enough used and clearly enough compared to Volhard and Fahr s[12] pathological classification to make an elaboration on the terminology of classification of nephritis in children unnecessary The forms of Bright s disease encountered in children are approximately the same clinically and pathologically as those found in adults but they differ materially in their frequency of occurrence Arteriosclerotic Bright s disease is the common form in adults And in other types in that age group the chronic forms predominate and are often complicated by cardiovascular changes In children the great majority of cases are acute hemorrhagic Bright s disease Structural cardiovascular changes occur but seldom and arteriosclerotic Bright s disease is rarely encountered There is in addition a rare disease peculiar to the younger group usually designated as congenital interstitial nephritis or renal rickets

In this chapter the authors wish to consider acute hemorrhagic nephritis as it occurs in children For the pediatrician it is particularly important as it constitutes approximately 75 per cent of the cases of nephritis occurring in the age group with which he is concerned Secondly there is a very definite syndrome which in about 8 per cent of the cases culminates in death unless the progress of the syndrome is checked by therapy which has been shown to be specific and peculiarly effective

Course of the Disease —The usual case follows an upper respiratory infection by an interval of one to three weeks Puffiness is noted about the eyes The urine is bloody and scanty sometimes to the point of anuria and of high specific gravity Pallor appears and the appetite suffers The albumin and sediment are as given by Addis in acute hemorrhagic nephritis Blood analyses may show though not necessarily high values for nitrogen Then in certain

cases central nervous system symptoms ensue These are headache visual disturbances vor
frequently a slowing of
convuls ons and coma
the name pseudo or convulsive uremia To them are attributed the fatalities in the acute stage of this disease

Edema is present It is not the marked pitting edema of nephrosis or the later stages of glomerular nephritis It gives one the impres



F G 157 —Medullary cone phase compress on of medul ary structures flattened con volut ons nd s n t su (Oxford Med c ne courtesy of the Oxford Univ Press)

sion of being intracellular not the shifting intercellular edema of subcutaneous tissue spaces *and body cavities* This differential type of edema exists in the brain The optic disks may show papilledema The brain is firm It weighs 25 to 30 per cent more than is normal for the age The dura is tense the convolutions are flattened and the ventricles are compressed to appear nearly as slits when the brain is sectioned There is every in lication of the rapid development of increase in the volume of the brain with

increased intracranial pressure Figure 155 shows the medullary cone phase with the medulla compressed into the foramen magnum

The blood pressure is elevated or is rapidly rising The rapidity of the rise is of as much importance as the actual height The amount of blood in the urine and the retention of nitrogenous substances are not reliable indices of the severity of the condition The evidence of impending cerebral symptoms is best indicated by the course of the blood pressure and the degree of oliguria

Whatever the major cause, clinical experience shows that the rise in blood pressure parallels the severity of the cerebral symptoms A fall in blood-pressure alleviates them Possibly the same is true of intracranial pressure The beneficial effects of the withdrawing of spinal fluid argue for such a view Certainly intracranial pressure is elevated with the presence of these symptoms But the evidence concerning the course and actual height of the intracranial pressure is not clear because of the difficulty of obtaining reliable measurements Sometimes very little fluid can be obtained by lumbar puncture and in the procedure there is the danger of incarceration of the edematous brain and compression of the medulla The evidence is clear as regards blood pressure, its course is easily followed and means of lowering it are free from danger In the treatment developed by one of the authors and discussed *in the following paragraphs* attention has been focussed on the blood-pressure

Magnesium Sulphate Therapy —Some years ago, Fisher[6] demonstrated that the blood pressure in acute nephritis could be lowered by the intravenous injection of a hypertonic salt solution consisting of 10 gm $Na_2CO_3\,10H_2O$ + 14 gm NaCl per liter of water Sub

sulphate But the physiological action of NaCl and $MgSO_4$ are such as to indicate the use of the latter salt The NaCl solution

such retention follows $MgSO_4$ The importance of the Na ion in water balance would lead one to expect this With the existence of cerebral edema the authors prefer to avoid the employment of a sodium salt

In order to prevent the necessity of repeated intravenous injections magnesium sulphate is given by mouth and rectum to such extent as to cause catharsis The dose is 1 to 2 ounces of 50 per cent $MgSO_4\,7H_2O$ every four hours This is effective in preventing a

subsequent rise in blood pressure and is an important part of the treatment Indeed, in mild cases such oral and rectal administration is alone an efficient means of preventing the development of cerebral symptoms

As an illustration of the course and treatment the case from which Fig 159 was taken is quoted

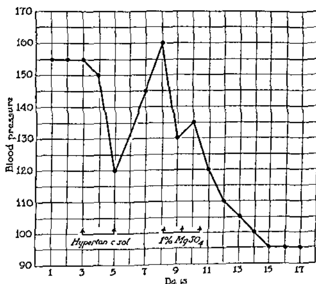


Fig 158 —Effect of hypertonic salt solution and 1 per cent $MgSO_4$ intravenously on blood pressure

The patient R K aged six years) was admitted to the hospital with

remaining at n 1 -
symptoms
subsequent

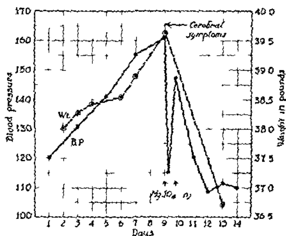


Fig 159 —Acute hemorrhagic nephritis with cerebral symptoms the effect of $MgSO_4$ on blood pressure and weight

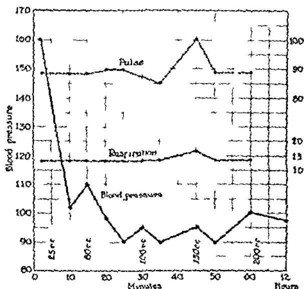


Fig 160 —Immediate effect of intravenous $MgSO_4$ on blood pressure pulse and respiration

Figure 160 shows in detail the effect of magnesium sulphate intravenously on blood pressure pulse and respiration

Blackfan and McKhann[3] have introduced intramuscular injection of magnesium sulphate instead of the intravenous method of administration The dose by this route is from 4 to 10 cc of a 25 per cent solution of $MgSO_4 \cdot 7H_2O$ If the blood pressure does not fall the injection is repeated (Fig 161)

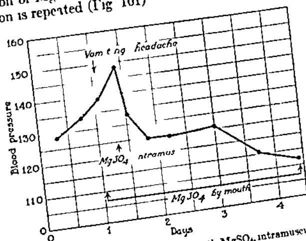


Fig 161 —Acute hemorrhagic nephritis treated with $MgSO_4$ intramuscularly and by mouth

In using magnesium sulphate as outlined above, toxic symptoms are not encountered but one should know, when using it in this manner the symptoms of overdosage The particularly important symptom is alteration in respiration at first a slowing and irregularity and then cessation Give to 10 cc of 3 to 5 per cent $CaCl_2$ solution intravenously is the antidote

The Physiological Action of Magnesium Sulphate —Such are the empirical facts At the present time we cannot be sure of the explanation

Meltzer,[8,9] in using magnesium sulphate in the treatment of tetanus and as an anesthetic ascribed its action to a synaptic inhibition to the passage of nerve impulses To be sure, his doses were usually larger than the doses given here and perhaps it is not fair to suggest a similar physiological action Yet he cites a case of tetanus in which 10 cc of a 25 per cent solution were given intramuscularly every six hours, and he produced anesthesia in 1 case by giving 180 cc of a 6 per cent solution to a man of 160 pounds Reduce this to the 40 pounds of a child and we find it equivalent to 135 cc of 2 per cent $MgSO_4 \cdot 7H_2O$ or 1 per cent $MgSO_4$ But even should some such narcotic effect be present, it seems certain that this cannot account for the entire picture

Lazard[7] in the treatment of eclampsia uses 20 cc of 10 per cent $MgSO_4 7H_2O$ repeating the dose usually every twelve hours This is very similar to the authors dosage He ascribes the beneficial effect to reduction of brain volume and intracranial pressure He does not state whether the effect is a primary reduction of intracranial pressure or a secondary effect following the lowering of the blood pressure

Clinical evidence favors the view that increased intracranial pressure is the cause of the elevated blood pressure But it seems justifiable to question the possibility of intracranial pressures in nephritis sufficiently high to cause the observed elevations in blood-pressure Experimentally it requires an intracranial pressure of at least 800 mm of water to produce such elevations in blood-pressure Available data would lead one to believe that such pressures are not attained in acute nephritis Against this argument the point has been made that the observed spinal fluid pressures may not correctly indicate the intracranial pressure, the latter being high possibly interferes with the free passage of fluid

Fisher ascribed the beneficial effects of his solution to its alkalinity and hypertonicity His views concerning the alkalinity do not seem tenable Of course his solution is hypertonic (0 27 molar) and if its action is due to an osmotic effect would tend to reduce the cerebral edema Weed and McKibben[13] believe that the reduction of brain volume following the injection of a hypertonic salt solution is due to such osmotic action But one encounters considerable difficulty in estimating the osmotic action of a bivalent salt such as magnesium sulphate Calculated on a molar basis it is hypotonic, calculated on the basis of ionic strength it is probably hyper tonic Further it is known from the effect of magnesium salts on the solubilities of other salts and proteins that the magnesium ion has a unique action At the present time it seems that the way in

not shown constriction though the retinal veins have been congested But should there be a capillary constriction particularly if more generalized than a constriction of the renal vessels that in itself might be the primary cause of the hypertension with cerebral edema a secondary sequence Possibly magnesium sulphate acting as a capillary dilator effects the blood-pressure and thus the cerebral symptoms

Presumably the oral and rectal administration of magnesium sulphate is effective through the dehydrating action

Figure 160 shows in detail the effect of magnesium sulphate intravenously on blood pressure, pulse and respiration.

Blackfan and McKhann[3] have introduced intramuscular injection of magnesium sulphate instead of the intravenous method of administration. The dose by this route is from 4 to 10 cc. of a 25 per *cent solution of $MgSO_4 \cdot 7H_2O$. If the blood-pressure does not fall* the injection is repeated (Fig. 161).

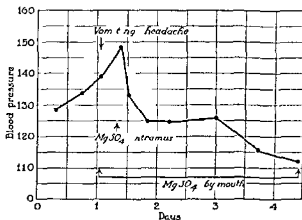


Fig. 161.—Acute hemorrhagic nephritis treated with $MgSO_4$ intramuscularly and by mouth.

In using magnesium sulphate as outlined above, toxic symptoms are not encountered but one should know, when using it in this manner, the symptoms of overdosage. The particularly important symptom is alteration in respiration: at first a slowing and irregularity and then cessation. Five to 10 cc. of 3 to 5 per cent $CaCl_2$ solution intravenously is the antidote.

The Physiological Action of Magnesium Sulphate.—Such are the empirical facts. At the present time we cannot be sure of the explanation.

Meltzer[8,9] in using magnesium sulphate in the treatment of tetanus and as an anesthetic ascribed its action to a synaptic inhibition to the passage of nerve impulses. To be sure, his doses

muscularly every six hours, and he produced anesthesia in 1 case by giving 180 cc. of a 6 per cent solution to a man of 160 pounds. Reduce this to the 40 pounds of a child and we find it equivalent to 135 cc. of 2 per cent $MgSO_4 \cdot 7H_2O$ or 1 per cent $MgSO_4$. But even should some such narcotic effect be present, it seems certain that this cannot account for the entire picture.

Lazard[7] in the treatment of eclampsia uses 20 cc of 10 per cent $MgSO_4 7H_2O$ repeating the dose usually every twelve hours. This is very similar to the authors' dosage. He ascribes the beneficial effect to reduction of brain volume and intracranial pressure. He does not state whether the effect is a primary reduction of intracranial pressure or a secondary effect following the lowering of the blood pressure.

Clinical evidence favors the view that increased intracranial pressure is the cause of the elevated blood pressure. But it seems justifiable to question the possibility of intracranial pressures in nephritis sufficiently high to cause the observed elevations in blood pressure. Experimentally it requires an intracranial pressure of at least 800 mm. of water to produce such elevations in blood pressure. Available data would lead one to believe that such pressures are not attained in acute nephritis. Against this argument the point has been made that the observed spinal fluid pressures may not correctly indicate the intracranial pressure, the latter being high possibly interferes with the free passage of fluid.

Fisher ascribed the beneficial effects of his solution to its alkalinity and hypertonicity. His views concerning the alkalinity do not seem tenable. Of course his solution is hypertonic (0.27 molar) and if its action is due to an osmotic effect would tend to reduce the cerebral edema. Weed and McKibben[13] believe that the reduction of brain volume following the injection of a hypertonic salt solution is due to such osmotic action. But one encounters considerable difficulty in estimating the osmotic action of a bivalent salt such as magnesium sulphate. Calculated on a molar basis it is hypo-

[illegible]

not shown constriction though the retinal veins have been congested. But should there be a capillary constriction particularly if more generalized than a constriction of the renal vessels, that in itself might be the primary cause of the hypertension with cerebral edema a secondary sequence. Possibly magnesium sulphate acting as a capillary dilator effects the blood pressure and thus the cerebral symptoms.

Presumably the oral and rectal administration of magnesium sulphate is effective through the dehydrating action

ven

of magnesium sulphate instead of the intravenous method of administration The dose by this route is from 4 to 10 cc of a 25 per cent solution of $MgSO_4$ $7H_2O$ *If the blood pressure does not fall,* the injection is repeated (Fig 161)

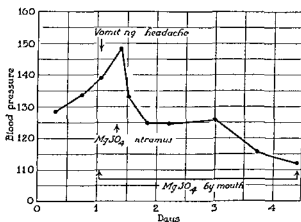


Fig 161 —Acute hemorrhagic nephritis treated with $MgSO_4$ intramuscularly and by mouth

In using magnesium sulphate as outlined above toxic symptoms are not encountered but one should know, when using it in this manner, the symptoms of overdosage The particularly important symptom is alteration in respiration at first a slowing and irregularity and then cessation Five to 10 cc of 3 to 5 per cent $CaCl_2$ solution intravenously is the antidote

The Physiological Action of Magnesium Sulphate —Such are the empirical facts At the present time we cannot be sure of the explanation

Meltzer,[8 9] in using magnesium sulphate in the treatment of tetanus and as an anesthetic, ascribed its action to a synaptic inhibition to the passage of nerve impulses To be sure, his doses

muscularly every six hours, and he produced anesthesia in 1 case by giving 180 cc of a 6 per cent solution to a man of 160 pounds Reduce this to the 40 pounds of a child and we find it equivalent to 135 cc of 2 per cent $MgSO_4$ $7H_2O$ or 1 per cent $MgSO_4$ But even should some such narcotic effect be present, it seems certain that this cannot account for the entire picture

CHAPTER XLII

FUNDAMENTAL STUDIES ON THE PHARMACOLOGY OF MERCURY DIURETICS *

By RAYMOND N BIETER M D PH D

AND

HAROLD N WRIGHT M S PH D

GENERAL ACTION OF DIURETICS

Introduction —Studies were made in the Pharmacological Laboratory of the University of Minnesota under the direction of [illegible] produced in blood [illegible] means of drugs [illegible] studied with the ultramicroscope and also by means of other methods of experimentation Hirschfelder and Wright[1 2 3] have shown that a number of antiseptic drugs, including arsphenamine and mercurochrome produce changes in the ultramicroscopic picture of the particles of rabbit s plasma In general they have interpreted their results to mean that the drugs studied are adsorbed by the plasma particles In so far as mercurials were included in their study their findings are confirmed by the studies herein reported

The present chapter has to do with a study of several mercury preparations, with particular reference to the organic mercury diuretic drugs, namely, salyrgan and novasurol † The attempt was made to study the fundamental processes involved in the production of their therapeutic action

Diuretics may be assumed to act in one or more of the following ways (1) Changes in the physico chemical state of the blood and tissue colloids, (2) changes in the blood flow and permeability of glomeruli, and (3) changes in tubular permeability While it would appear likely that changes in the kidney play a considerable rôle in the actual excretion of the urine, it would seem necessary, at least in some cases, that changes should take place first in the tissue and blood colloids, whereby water presumably bound to

* A summary of the findings here n reported was read before the Minnesota Branch of the Society of Experimental Biology and Medicine (Proc Soc Exp B ol and Med 26 551 1929 1930) and the American Pharmacological Society Chicago Meeting March 1930

† The salyrgan and novasurol used in these studies were obtained through the courtesy of the H A Metz Laboratories Inc New York

Conclusion.—*Unsatisfactory as our present knowledge of the* physiological action of magnesium sulphate is, its use as outlined gives us a most effective therapeutic measure for successfully treating the frequently fatal condition of "pseudo or convulsive uremia" in acute glomerular nephritis

REFERENCES

1 ADDIS, T 1925 A clinical classification of Bright's disease, J Am Med Assn, 85, 163–167

2 ALDRICH, C A 1930 Clinical types of nephritis in childhood, J Am [illegible]

[illegible] 1930 Nephritis in childhood, [illegible]

[illegible] 923 The effect of a 2 per cent magnesium sulphate solution on the cerebral symptoms in acute nephritis, Trans Am Ped Soc, 35, 197–201

[illegible]

8 MELTZER, S J 1916 Inhibitory properties of magnesium sulphate and their therapeutic application in tetanus, J Am Med Assn, 66, 931–934

9 MELTZER, S J 1916 Anesthesia in human beings by intravenous [illegible]

[illegible] INTOSH, [illegible] JOHN- [illegible] Bright's [illegible] 386 [illegible] kun- [illegible] chert, [illegible] ebro-spinal fluid following intravenous injection of solutions of various [illegible] ions, Am J Physiol, 48, 512–530

plasma particles were definite and striking in all cases where either drug was used These changes were as follows (1) An increase in the average size of the particles (2) what appeared to be a decrease in the number of particles visible and (3) an increase in their brilliance or refractiveness It was this change in brilliance that was so conveniently measured with the photometer These changes are in agreement with those occurring when a lyophilic colloid changes toward a lyophobic colloid

It very soon became evident that the per cent change in refractiveness as measured with the photometer varied and appeared to be greatest in those plasmas containing the drug that had been allowed to stand for several hours Examples of this can be noted in the following four plasmas

TABLE 88

Normal heparin plasma	Novasurol added	I[illegible]	Allowed to stand
R = 14	R = 15 0	4	½ hr
R = 21	R = 27 [illegible]	3	3 hrs
R = 20	R = 27 0		5
	Salyrgan added		
R = 21	R = 23 5	12	1 hr
	R = 26 0	1	hrs
	R = 27 5	31	5

This would indicate that these changes occur slowly and therefore time must be allowed to produce maximum effects Consequently in further experiments of this type the drugs were added to the diluted plasmas and readings of each were taken at one and a half and three hour intervals covering a period of up to ten hours In addition another series of readings was taken using mercuric chloride The solution of this drug was made up to 0 046 per cent so that its mercury content corresponded with that of novasurol Salyrgan has a slightly higher percentage of mercury than novasurol but no correction for this was made

Plasma of the Dog —Heparinized plasma was now collected from a series of frogs and from a number of dogs and the effects of the three mercury salts were studied on each plasma sample and compared to one another and to the normal heparin plasma The results of this series of experiments with the ultramicroscope proved the above suggestion namely that the changes were progressive They also brought forth another interesting point namely that with mercuric chloride the changes progressed most rapidly next in speed of action came novasurol and finally salyrgan showed the slowest rate of change This might be associated with the clinical fact that salyrgan is less toxic and safer to use than novasurol Table 89 shows a typical experiment upon one dog s plasma

the proteins (bound water) is released and becomes available for filtration

In carrying on studies of the blood plasma some means of preventing coagulation must be employed Therefore at the onset samples of blood were collected from Rana catasbiana into (1) Heparin ($\frac{1}{3}$ mg per cc of blood) (2) potassium oxalate (2 mg per cc) and (3) sodium citrate (2 5 mg per cc) These samples were centrifuged the plasma pipetted off and diluted 1 to 5 with specially prepared particle free 0 75 per cent physiological saline The diluted plasmas were then compared with each other and with plasma collected in the same manner but without the use of an anticoagulant under the ultramicroscope From these experiments *it was found that blood the coagulation of which was prevented* with heparin yielded a plasma closest to the normal where no anticoagulant was used In other words their ultramicroscopic appearances were almost the same For this reason heparin plasma has been considered the standard in further experiments

The criterion used to make these determinations was the general appearance of the particles that is whether they were large or small whether they reflected the light markedly or only slightly and whether Brownian movement was brisk or sluggish For determining the amount of light reflected that is the refractiveness of the field the wedge photometer of Hirschfelder and Wright was used This gives nearly quantitative comparisons between the various samples of diluted plasma with and without the addition of the mercury salts The photometer consists of the chamber of a long wedge colorimeter filled with an opaque solution (diluted non waterproof India ink) The wedge is moved across the top of the ocular of the ultramicroscope until the light cone is just completely obliterated This point in centimeters from the narrow [illegible] When more [illegible] ition a greater

[illegible] **Plasma of the Frog** The effects of novasurol and salyrgan were first studied upon *frog s plasma Both drugs were made up in 0 1 per cent* concentration in 0 75 per cent NaCl This gives 0 01 mg per 0 01 cc To 1 cc of frog s plasma diluted with 4 cc of 0 75 per cent NaCl solution was then added 0 02 to 0 04 mg of either novasurol or *salyrgan This amount of the drug is comparable to the* concentration produced when 1 to 2 cc of a 10 per cent solution of either drug is injected intravenously in a patient assuming that the circulating blood has a volume of 5 liters

Following this the *diluted plasmas and the diluted* plasmas plus novasurol or salyrgan were observed under the ultramicroscope and compared The changes in the ultramicroscopic appearance of the

Six hours later another sample of plasma was obtained from the same patient At this time the R was 18 2 or a 66 per cent increase in refractiveness *in vivo* During the twenty four hours previous to the administration of the novasurol the patient voided 175 cc of urine In the five hours following the novasurol the urine volume rose to 750 cc

Discussion of the Experimental Facts The changes in the particles of the plasma solutions described above namely an increase in size of the particles and a marked increase in their brilliance or refractiveness are changes that correspond with those occurring when a lyophilic (water loving) colloid becomes lyophobic (water repelling) According to Kruyt [4] these changes are due to two processes One is a decrease in the electric charge a change toward neutralization and the other is a decrease in hydration For complete precipitation of a protein solution these two changes must take place, either one may occur first but either alone is not sufficient In the precipitation of a protein in solution with ammonium sulphate the addition of the first small amount is thought to neutralize the charge and the addition of further large amounts dehydrates the protein particles and then precipitation occurs With a mercury salt these effects can be produced in the same manner

In our experiments we have used much smaller amounts of the mercury salts and no precipitation whatever has occurred In the light of what is known of the precipitation of proteins with salts as described above it is thought that the first thing occurring is somewhat of a neutralization of the electric charge But from what we know of this phenomenon it occurs rapidly Because our

inclined to believe that this involves a dehydration Further support for this belief is obtained from clinical experience with these mercury diuretics namely that they cause primarily an increase in the water output which however does not occur immediately after administration but shows a gradual increase reaching a

Sollmann that the diuretic effects were due primarily to the mercury ion

If the authors experimental findings mean a change in the

In this experiment the three drugs salyrgan, novasurol and mercuric chloride, in the percentage solutions described above, were added to one set of diluted plasma samples (dilution 1 to 40), 0.04 cc per cc of plasma, and to another set of diluted plasmas, 0.02 cc. per cc of plasma. In both series the results were identical except that in the plasmas receiving the smaller amounts of the drug, the changes occurred more slowly and did not progress quite as far in the seven and a half hours of the experiment. As can be seen from Table 89, mercuric chloride produced a maximum effect (an increase in the R of 45 per cent) in about three and a half hours, novasurol, a maximum effect (increase in R of 37 per cent) in about six hours, and salyrgan a maximum effect (increase in R of 28 per cent) in about seven and a half hours.

TABLE 89.—SHOWING THE EFFECTS OF SALYRGAN, NOVASUROL AND MERCURIC CHLORIDE UPON THE REFRACTIVENESS (R) OF THE HEPARINIZED PLASMA OF A DOG

Time 12 M	Normal	0.04 cc mercurial per cc plasma			0.02 cc mercurial per cc plasma		
		Salyrgan	Novasurol	$HgCl_2$	Salyrgan	Novasurol	$HgCl_2$
1 30 P.M.	R = 16	R = 17.5	R = 19.0	R = 21	R = 17.5	R = 19.2	R = 20.0
3 00 P.M.	R = 16	R = 18.5	R = 20.5	R = 22	R = 18.5	R = 20.0	R = 20.0
4 30 P.M.	R = 16	R = 20.0	R = 21.2	R = 23	R = 20.0	R = 21.0	R = 21.0
6 00 P.M.	R = 16	R = 19.5	R = 21.5	R = 23	R = 20.2	R = 22.0	R = 22.5
7 30 P.M.	R = 16	R = 20.2	R = 22.0	R = 23	R = 20.5	R = 22.0	R = 22.5

Kidney Extract From the Frog.—To study the effects of these drugs upon other body colloids the frog's kidney was selected. The kidneys were perfused free of blood and then ground in 0.75 per cent NaCl solution and centrifuged. The supernatant opalescent solution was then treated as the plasmas in the above experiments. The same changes were noted with these colloid solutions as with the colloids of the blood plasma, that is, the particles observed with the ultramicroscope seemed to decrease in number but to increase in size and refractiveness.

Plasma of Patients With Cardiac Decompensation.—Further studies were now conducted upon human cardiac decompensated patients. The material for these experiments was generously donated by Prof. George E. Fahr, of the Minneapolis General Hospital, Minneapolis, Minn. The results obtained in 1 patient are as follows. To a sample of plasma from heparinized blood, 0.02 cc. of novasurol, 0.01 per cent per cc. of plasma, was added. The normal plasma showed an R of 11. The plasma plus novasurol showed an R of 22.5 (100 per cent increase) at three hours and an R of 23 (120 per cent increase) at eight hours. This patient was given 1 cc. of novasurol intravenously at a time when the normal R was 11

The membranes used were viscose sausage casings of about ¼ to ¾ inch in diameter

Heparinized dog s plasma prepared as described above was used for these experiments To 10-cc plasma samples were added varying amounts of mercuric chloride made up in distilled water Because the effects noted with the ultramicroscope required from three to four hours to reach a maximum these plasmas were allowed to stand for this length of time Then they were dialyzed with occasional gentle shakings for periods of from one and a half to four hours In all of the experiments of this series the plasmas to which mercuric chloride had been added showed a greater amount of chloride in the dialysate than did the controls

Typical experiments run as follows

TABLE 91

	10 cc normal plasma Mg	0 + 5 mg HgCl$_2$ Mg	10 cc + ? 5 mg novasurol Mg
Chloride dialyzed in three hours	46 800	49 00	47 6
Per cent dialyzed	100 000	103 700	101 7
Chloride dialyzed in three hours	57 964	61 087	
Per cent dialyzed	100 000	105 400	

In the first experiment the plasmas were allowed to stand three hours before the dialysis was begun In the second experiment the plasma stood for four hours The chlorides were determined by the thiocyanate titration method of Volhard In all cases the results on the HgCl$_2$ plasma were corrected for the amount of chloride added The amounts of mercuric chloride and novasurol added to these plasmas to date have been much larger than the clinical concentrations used Further work is being done using

believed that these changes represent primarily a dehydration

2 These same drugs produce progressive decreases in the free surface of the plasma particles as measured by the ability of the plasma particles to adsorb rose bengal

3 From blood plasma to which novasurol and mercuric chloride have been added (to date in amounts larger than therapeutic doses) a greater amount of chloride can be dialyzed than from normal blood plasma

4 It is believed therefore that the mercury preparations act as diuretics due to their action upon body and blood proteins This action is thought to be a progressive dehydration and liberation of chlorides which are thus made more available for kidney excretion

electric charge and, more especially, if they mean a dehydration, the surfaces of these plasma particles ought to show changes.

Rosenthal[1] has shown that sodium oleate and bile salts, substances which lower surface tension, decrease the binding power of a protein in solution for rose bengal. Hirschfelder and Wright[1] have shown in a study of the behavior of antiseptics in albumin solutions that the amount of malachite green bound by a given mass of egg albumen decreases as the concentration of the protein increases. They interpret this as due to a dehydration of the protein micelles with increasing protein concentration and a corresponding decrease in the free surface.

It was, therefore, thought worth while to study the adsorption of this dye by the plasma protein particles before and after the addition of varying amounts of mercuric chloride, novasurol and salyrgan. A progressive decrease in the free surface of the proteins was found over a period of about six hours. An experiment of this type is shown in Table 90.

TABLE 90.—SHOWING THE PER CENT DECREASE IN FREE SURFACE OF THE PLASMA COLLOIDS OF A DOG PRODUCED BY $HgCl_2$, NOVASUROL AND SALYRGAN MEASURED BY THE ABILITY OF THE PLASMA COLLOIDS TO BIND ROSE BENGAL

Mg. per 100 cc. 1 to 40 diluted plasma	Per cent decrease in free surface														
	Mercuric chloride					Novasurol					Salyrgan				
Time	2	4	6	8	10	4	8	12	16	20	4	8	12	16	20
3 hrs.	6.3	7.0	10.7	12.7	12.7	0	0.8	0.8	2.0	2.8	0	0.4	0.8	2.0	2.8
5 hrs.	[illegible].3	9.3	12.7	15.0	16.0	0	0.8	1.2	3.2	4.0	0	0.8	1.6	4.0	4.8
8 hrs.	6.3	10.0	13.3	15.7	16.7	2	3.2	6.8	4.0	6.0	1.2	2.4	4.0	6.0	9.2

From the fact that the change in the free surface is progressive over a period of hours, paralleling the changes observed with the ultramicroscope and the clinical occurrence of the diuresis, it seems probable that the essential step is a slow release of bound water (dehydration of the proteins) which then becomes available for filtration.

One other important action of mercury diuretics is to increase the urinary output of chlorides. If the explanation of the ultramicroscopic readings above is a decrease in the electric charge and a dehydration, chlorides might also be liberated in this process and then become available for filtration. To study this phase of the problem, samples of plasma without and with additions of small amounts of mercuric chloride were dialyzed against distilled water.

CHAPTER XLIII

THE CLINICAL USE OF DIURETICS

By NORMAN M KEITH, M D

Introduction —The Choice of Diuretics —The author's interest in the subject of diuretics was primarily stimulated by the inadequacy of the accepted methods of treating renal edema In December, 1923, a patient under his observation, with chronic diffuse nephritis and general anasarca, failed to respond to the usual methods of treatment Knowing that calcium chloride had been used successfully abroad by Blum and others[4] in cases of edema, he decided to give it a trial in this instance The patient was given calcium chloride *for three periods, each of a week's duration During the first period,*

[illegible]

diets[19] have a lower content of salt and water than the so-called salt-free diet of Widal, and the author has found it to be an important adjunct to diuretics in the treatment of edema[1, 19] (Table 92)

Table 92 —Composition of Diets Low in Salt and Fluid

Type	Carbohydrate gm	Protein gm	Fat gr	Calories	Water cc	Sodium gm	Chlorine gm
Basal 'salt-free'	190	40	65	1500	1300	1 15	1 [illegible]0
1	150	40	80	1500	800	0 50	0 70
2	235	50	145	2500	900	0 77	0 68
3	300	60	120	2500	930	0 70	0 90
4	350	70	85	2500	850	0 68	0 85
5	345	80	90	2500	950	0 67	0 75
6	320	90	95	2500	860	0 65	0 78
7	275	100	110	2500	920	0 75	0 80

Later, ammonium chloride was substituted for calcium chloride, as it is less irritating to the stomach and just as effective as a diuretic In April, 1924, a patient with renal disease and marked

REFERENCES

n the colloid
nbination of
-431
tisepsis and
chemotherapy III The ultramicroscopic examination of neoarsphenamine and of certain antiseptics, and their effects upon protein solutions J Pharm and Exp Therap 39 13-37

3 ———— 1930 A wedge-photometer for quantitative comparison of ultramicroscopic particles Proc Soc Exp Biol and Med 27, 547-548

4 KRUYT H R 1927 Colloids, A Textbook, translated by H S Van Klooster, New York

8 ———— 1930 Studies on the colloid chemistry of antisepsis and chemotherapy IV The duplication *in vitro* of the interference phenomenon in combination chemotherapy J Pharm and Exp Therap, 39 39-57

the abdominal organs satisfactory diuresis can be produced by the procedures mentioned They have also proved effective in myxedema

The Prevention of Toxic Symptoms —The occurrence of obvious toxic effects such as stomatitis diarrhea and dermatitis was very *infrequent They occurred relatively more often in cases of hepatic* insufficiency than in any other single group of cases and usually followed injections of merbaphen Mersalyl very rarely caused general toxic symptoms although in a few cases local necrosis occurred at the site of intravenous injection This usually can be avoided by diluting the drug in 10 to 20 cc of physiological solution of sodium chloride or in the same amount of the patient s own serum The most frequent toxic effect was definite renal insufficiency [a] clinical symptoms of a toxic nature were usually absent As one would naturally surmise renal insufficiency occurred most frequently in cases of glomerulonephritis but it also occurred in a considerable number of cases of hepatic disease Fortunately it was a temporary dysfunction in the majority of instances the value for blood urea fell to normal and the excretion of phenolsulphonephthalein rose before dismissal of the patients Severe acidosis when caused by ingestion of ammonium chloride or calcium chloride may be accompanied by marked renal insufficiency By careful administration of these salts such an untoward event can be prevented

so

am

sometimes occur but disappears quickly when administration of the salt is discontinued Dehydration resulting from both a low intake

there seems to be less tendency to toxic reactions than in cases in which there are either renal or hepatic lesions This finding is in *agreement with those of previous observers*

Experiments on Normal Subjects In order to obtain under controlled conditions more definite information as to the action of diuretics a series of experiments was carried out on 12 normal persons (Fig 162) The diets were the same as those given to patients with edema with the addition of 800 cc of fluid A control period

under investigation was withheld During ... the volume of urine the total excretion of chlorides the total fixed base in the urine and the total nitrogen in the urine were determined daily The trial substances administered were ammonium

general anasarca was given ammonium chloride with good diuretic response[16] In 1933 the patient was still free from edema and was in good general health If edema persisted in any case after the use of these acid salts a trial was made of the organic compound of mercury merbaphen The combined effect of ammonium chloride and merbaphen was often more striking than when these substances were administered singly[17 20] Chronic lipoid nephrosis was the type of renal disease that responded most satisfactorily to these diuretics although in certain cases of chronic glomerular nephritis with edema a satisfactory response was obtained In cases of the latter type care must be taken that the concentration of urea in the blood is not greatly increased and that the organic compound of mercury does not cause hematuria In 1 case in which hema turia occurred after the first injection of merbaphen an injection

nitrate However the experiments represented by Fig 102 in volved 12 normal persons only Actually in practice of these acid salts which ... been
the most eff ... lts
indicate tha ... a
specific diuretic action In this connection it should be pointed out that Osman produced diuresis in cases of renal edema by the use of large doses of alkaline salts

Clinical Types of Edema In cases of renal edema in which acid salts and organic compounds of mercury are contraindicated com pounds of caffeine such as synthetic theophyllin (theocin) and euphyllin may b ... Bright noted that digi talis might also l
in the author s e
pre ence of cardiac decompensation

The significance of diuretics in the treatment of cardiac edema is becoming generally recognized One of the author s patients who ... of mercury
fluid in
liters[18]
he man
nsation
by the
use of diuretics

In three conditions in which ascites occurs namely cirrhosis of the liver polyserositis or Pick s disease and malignant disease of

and disappears quickly after administration of the nitrate is discontinued[10]

In later experiments on dogs and normal persons the combined effects of ammonium chloride or ammonium nitrate and organic compounds of mercury were studied Excretion of water chloride *and fixed base was much greater than when these were administered* singly

The Action of Diuretics —In any consideration of the action of these diuretics a general and a renal effect must be considered[7,9] The acid chlorides alter the acid base equilibrium and increase the concentration of plasma chloride[16,20] Both factors aid diuresis[7,8]

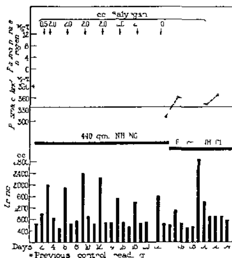


FIG 163 —A case of cirrhosis of the liver with ascites in which the patient was aged nineteen years Restoration of failing diuresis increase in plasma chlorides by the substitution of ammonium chloride for ammonium nitrate are shown

When the concentration of plasma sodium was increased by ingestion of a sodium salt spontaneous polyuria occurred Blumgart[5]

acetate digitalis sucrose, urea euphyllin, sodium nitrate, ammonium nitrate, ammonium chloride and merbaphen The results are shown in Fig 162 It should be noticed that ammonium acetate and digitalis had little diuretic effect that urea produced typical diuresis of water and that euphyllin and sucrose caused slight increase of excretion of water chloride and fixed base Sodium nitrate caused an increase in excretion of water chlorides and fixed base, whereas ammonium nitrate caused similar, but increased excretion Ammonium chloride likewise produced marked excretion of water fixed base and chlorides, excretion of chloride was due in part to the large intake of chloride Of all these nine substances, merbaphen produced the most rapid diuresis [15b]

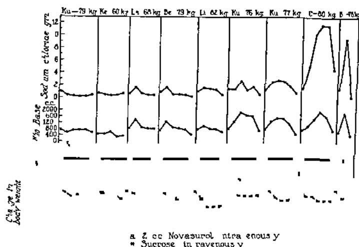


Fig 162 —Comparison of the act on of certain substances on the output of water chlorides and fixed base in the urine of normal persons The da ly intake of food and water was the same throughout each experiment

The excretion of nitrate in the urine following ingestion of ammonium nitrate by a normal person amounted to from 80 to 90 per cent [22] The concentration of nitrate nitrogen in the blood plasma rose to from 2 to 3 mg per 100 cc The excretion of nitrate was similar in cases of chronic nephrosis but the concentration in the blood increased In 1 case of diffuse nephritis the nitrate produced diuretic effects but failed to be excreted in suitable amounts so that marked retention of nitrate occurred in the blood, the concentration reaching 19 mg per 100 cc In spite of the toxic effect the patient made a good recovery Since this occurrence the use of a simple method devised by Whelan for determining the nitrates in the blood has allowed such toxic effects to be prevented Methemoglobinemia occurs rarely does not cause inconvenience

The ideal diuretic has yet to be discovered In the last fifteen years, experimental work and clinical observation have added much to knowledge as to the action and therapeutic results of various types of diuretics This should give much hope for continued development in the future

References

1 Barnick E G, and Keith N M 1928 The treatment of nephritis and nephrosis with edema J Am Med Assn, 91 1944–1952
2 Barker M H 1932 Edema as influenced by a low ratio of sodium ... Assn 98 2193–2197
... the effect of diuretics in ... 2020
... L action diurétique ... et mém Soc méd d ...

... Brown, M C 1932 The effect of diuretics on water and salt metabolism Trans Assn Am Phys, 47, 304–307
6 ...

... The action of specific diuretics J Am Med Assn, 93 2016–2018
9 Engel, K and Epstein, T 1931 Die Quecksilberdiurese, Ergebn d inn Med u Kinderh, 40, 187 271
10 Eusterman, G B, and Keith N M 1929 Transient methemoglobinemia following administration of ammonium nitrate Med Clin North America 12, 1489–1496
11 ... compos...
12 ... M 1933 ... 100, 251–254
13 Herrmann, G, Schwab, E H, Alvarez J A and Cate M E 1933 Concomitant clearances of creatinine, d xylose urea and chlorides during diuresis in congestive heart failure, Proc Soc Exp Biol and Med, 30 1375–1379
14 Herrmann, G, Stone, C T, Schwab E H and Bondurant W W 1932 Diuresis in patients with congestive heart failure, J Am Med Assn, 99 1647 1652
15a ...

... novasurol in cases of nephritis with edema, J Am Med Assn, 85, 799–806
18 Keith N M, and Jacobs, M I 1926 The use of diuretics in cardiac edema Med Clin North America, 10 605–610
19 ... use ...

... 43 288–291

expressed the belief that an optimal concentration of sodium in addition to that of chloride in the plasma is important for diuresis and may in part be the reason for production of diuresis by alkaline salts Stehle in his experimental work with compounds of mercury stressed their general tissue action because there is a definite latent period before diuresis begins The experiments of Govaerts and of Christian and Bartram [6] on the other hand emphasized the marked renal action in diuresis caused by mercury Hartman[12] has tried intravenous injection of acacia in stubborn cases of lipoid nephrosis and has been able to produce diuresis In his opinion the diuresis was caused by raising the osmotic pressure of the plasma

Recent advances in renal physiology suggested that different types of diuretics might have specific actions on the glomerulus or tubule
able to show
effects on t
similar results in cases of cardiac disease with edema Because there is some question as to the exact significance of creatinine clearance by the kidney the author does not feel that the results of Schmitz and Herrmann have yet established the fact that mercury exerts its diuretic action by diminishing reabsorption of water by the tubules and euphyllin its diuretic action by increasing glomerular excretion Experiments of Smith and his co workers [10] with the renal excretion of certain sugars has suggested that these sugars pass through the glomerulus and are not reabsorbed by the tubules It is of interest that Herrmann[13] has found that the ratio of the creatinine to the xylose clearance is increased when mersalyl is used but little altered when caffeine and compounds of digitalis are used

Potassium salts have been known for many years to have a dehydrating effect on the animal organism Wilks and Taylor in 1863 [29] administered potassium nitrate by mouth in a case of nephritic edema with success The toxic effects of potassium salts when administered by vein deterred physicians for many years from using them in clinical medicine Barker[2] has introduced the use of potassium chloride by mouth in cases of cardiac and renal edema He has seen no toxic effects and the diuretic effect in some cases has been satisfactory The author has confirmed his findings in a few cases This action of potassium chloride suggested to the author a trial of potassium nitrate in place of ammonium nitrate

has been present and it has proved a valuable addition to diuretic drugs Further studies as to its action on the blood and urine are being carried out

CHAPTER XLIV

NERVOUS RENAL CONTROL AND RENAL SYMPATHECTOMY

By LEONARD G. ROWNTREE, S.D., M.D.

WALTMAN WALTERS, Sc.D., M.D.

AND

WINCHELL McK. CRAIG, M.S., F.A.C.S.

Introduction.—What part do the renal nerves particularly the ... What are the ... such a step

The interest in this subject with one of the authors (R.) dates back a long time. Some twenty years ago experiments were carried out in the laboratory of Dr. John Abel in the course of which subsequent to injection of phenolsulphonephthalein into rabbits and dogs one kidney was denervated and the output and character of of the urine from the two sides contrasted. From the denervated side striking diuresis was obtained the urine being of low specific gravity and of a pale pink color indicating a slight alkalinity, whereas from the intact kidney the amount of urine was small the specific gravity high the color yellow and the reaction acid.

... of the renal nerves outside the kidney and what is the distribution of the ...

... the volume of urinary ... what is the nervous effect upon the composition of the urine and on the total amount of work done by the kidney?

3. Hitherto the leading principle for much research clinical as as well as physiological has been a comparison of the composition of the urine with that of the blood. On this basis light has been thrown upon important phases of renal function. The development at present points toward a period of concentrated interest in the balance between nervous and hormone regulation.

183-197

28 WIDAL, F AND JAVAL, A 1903 La cure de déchloruration Son

researches (Smirnow and others and most recently Kaufmann and Gottlieb[11]) demonstrating the presence of an extensive unmyelinated innervation of the parenchyma of the tubular epithelial cells in addition to the well recognized vascular innervation. Smirnow's figures are frequently reproduced f r by Stohr and by Mollen

heb

rve receptors

t the clinical

and experimental results in regard to the t renal pain. While there is no doubt about the producti n of p in the renal pelvis and about the absence of pain s from the renal parenchyma it is difficult to know to what extent p in produced by the renal capsule. Surely stretchin the c ul is sometimes concomitant with pain in the renal region th r times not and renal pain might be present when the kidne contracted and the capsule adherent. There is full agreement that pull upon the kidney is painful, and surgeons of excellent judgment consider much renal pain as originating in the prerenal p rit neum

Diuresis Following Denervation of the Kidney The mplete sometimes fatal, reflex anuria well known from instances of stone in one renal pelvis and also observed after the introduction of a ureteral catheter in the pelvis is of theoretical importance as

contr l of renal irculation

to this situation the experi

perivascular denervation or

absolute denervation through autotransplantation compatible with satisfactory renal function and normal life (Quinby Milliken and Karr,[16] Williamson[17] and others). The next important question concerns the interpretation of the diuresis following complete denervation or rather of the changes in the excretion of solids concomitant with the diuresis. Marshall and Kolls[5] found these changes fully explainable on the basis of alteration of renal blood flow and saw no necessity to assign any specific secretory inhibitory action to the splanchnic nerve. Cushny[3] took the same standpoint. The excretory features studied by Marshall and Kolls besides urine volume, included the elimination of phenolsulphonephthalein creatinine urea and chlorides. The absolute elimination of phenolsulphonephthalein and creatinine was not altered by the diuresis following one sided section of the splanchnic or homolateral extirpation of the adrenal while urea and chlorides were eliminated in increased amounts the chloride concentration even being higher on the denervated side. This high chloride concentration together with high urine volume on the operated side is particularly marked

alt

the dener-

vat

umerous in

ves

tory results

4 Focussing the interest upon the possibility of influencing the nervous mechanism of the kidney surgically or otherwise different problems present themselves Three different indications claim consideration (*a*) Relief of pain (*b*) improvement of function by relaxation of spasm and (*c*) relief of anuria of reflex nature so called reno-renal reflex anuria

To none of these question is it possible at present to give a satisfactory answer

Innervation of the Kidney Our anatomical knowledge is presented by Renner in the monographic work by Muller [18] by Stohr [23] and by Kuntz [1] *Among the abdominal organs the kidneys possess* a nerve supply which in richness is second only to the adrenals According to Quinby [21] this cannot be fully severed by perivascular stripping alone some fibers running within the vessel walls Complete denervation can be obtained only by section of the renal pedicle followed by reimplantation of the kidney by vascular suturation Sangres gives the following description The extrinsic nerve supply of the kidney is derived from the renal plexus which extends from the aortic plexus along the renal artery to the hilum of the kidney The renal plexus is made up of branches arising from the center of the semilunar ganglion the lesser splanchnics and major splanchnics a branch arising from the first lumbar ganglion and small branches arising from the small ganglion which lies on the posterior aspect of the superior mesenteric artery The renal plexus is also joined by one or more slender rami from the lumbar portion of the sympathetic trunk according to some authors Vagus branches run directly to the renal plexus in many but not in all cases *Direct vagus branches seem to occur more commonly on* the right than on the left side Preganglionic fibers supplying the kidney are present in all the splanchnic nerves The afferent fibers supplying the kidney are derived from the fourth to the twelfth thoracic segments but clinical evidence seems to indicate that they are derived mainly from the tenth eleventh and twelfth thoracic segments

The innervation has been analyzed in detail by Ellinger and Hirt [5] who describe three nerve groups (1) The greater splanchnic (2) the lesser splanchnics (nervi renales superiores) and (3) fibers leaving the sympathetic trunk in the lower thoracic and lumbar segments (nervi renales inferiores or unteren Grenzstrangfasern) Ellinger and Hirt claim a separate functional effect by each nerve

... le of the vagus

10)

ibers

o the

renal

pelvis and to the capsule is well known Of special interest are the

At least a suggestion of the normal stimulus for the reflex regulation of urinary secretion may be seen in another result obtained by Bayliss and Fee These workers used an innervated kidney-heart lung preparation, the kidney was left with intact nerve supply

kidney provided by the heart lung preparati n in re sed as did the urine flow, changes possible only thr ugh efle dilatation of the vascular bed of the kidney Simil r refl v ular dilatation in the kidney has been obtained by Hev in n foll wing increased pressure within the carotid sinus (See Volh r l p ge 391)

Clinical Aspects —During the wave t ntl ver perivascular sympathetic stripping which swept about 1920, Papin and Ambard[70] carried out the first ren l th t my on man The operation was undertaken f r rel t pain Six instances were reported in 1921 (republish th ntry 1924) The conditions for which the operation was un ke en were diagnosed as slight hydronephrosis and renal pto s Th p un suffered by these patients the authors found to be ex tl eprod ed by distending the renal pelvis during pyelograph l ur p t ents were relieved of their pain, 2 were not benefite l b t e p rati n The operation consisted in resection of the nerve nter lly and posteriorly to the renal pedicle This necessitated extensive freeing of the kidney At the end of the operation the artery and vein should be completely stripped of all surrounding nerve filaments Decapsulation and nephropexy were performed is a part of the operation in all instances The operation was not considered difficult, but care had to be exercised not to injure the renal vein

r ordinary ymptoms Legueu unilateral

impairs its functional capacity, it may be done tentatively as a preliminary procedure Harris and Harris[7] of Sydney, in the last five years have performed this operation for the relief of renal pain on 28 patients with most satisfactory results They have elaborated the painful condition in which they have found the operation indi-

Marshall and Crane[14] to previous results added data as to the behavior of carbonates ammonia sulphates and phosphates The carbonates behaved much like the chlorides ammonia like creatinine and sulphates and phosphates like urea Ellinger and Hirt[6]

ments demonstrate that similar diuresis with its sequences does not occur after section of the greater splanchnic nor of the fibers from the lower sympathetic trunk (nervi renales inferiores) To

stic action

ting excre

the details

has been

presented

Stimulus for Reflex Regulation of Urinary Secretion —What is the central or reflex stimulus whereby the nervous control of urinary secretion is brought to function? Bieter in this volume discusses the reflex arch and exemplifies the mechanism But cooling of the skin or pinching the hind limb surely does not represent the normal stimuli by which continuous control is exercised How far has the balance between nervous and hormone control been elucidated? Just as in blood pressure studies investigative efforts have been concentrated upon the balance between adrenalin discharge and splanchnic stimulation so the problem of the control of urinary secretion centers on the splanchnic and the pituitary though the adrenals too have to be considered (Tournade and Hermann[5]) As *in the studies of the regulation of blood pressure* (Volhard page 388) so even here development in experimental technique made possible more precise formulation of the problem Studies by Starling and Verney[22] on the isolated kidney provided with cir

that the

does in a

imentally

low in total solids

that of the perfus

erfusion fluid both

in experiments by Starling and Verney and by Bayliss and Fee[1] increased the chloride concentration in the urine and augmented greatly the total amount of chlorides excreted The addition of blood fresh from an animal with preserved circulation through the head produced the same effect in the experiments of Bayliss and Fee Verney[26] by including the heart lung kidney preparation also the head and neck likewise registered increased concentration of the chlorides but failed to obtain an increase in the absolute amount

twenty years duration An adenocarcinomatous polyp was removed from the duodenum Convalescence was uneventful Two months later he developed a chronic infectious arthritis and returned to the clinic for

attributed to the renal pelvic resection alone

cated as a clinical entity for which they offer the name renal sympathetico tonus These authors have further performed the operation once for 'essential hematuria and once for parenchymatous nephritis For conditions of this latter type Tietze[4] emphasized the satisfactory results obtained by decapsulation alone In the Mayo Clinic, 2 of the authors (W and C) have performed renal sympathectomy in selected cases

From the point of view of the internist *renal sympathectomy* presents quite a different problem *viz* the increase of urinary secretion through release of vasoconstriction During the last five years ever since results were obtained through sympathectomy in cases of arthritis the possibility of increasing the circulation in renal disease by the use of a similar operation has seemed worth considering Consequently it was advocated by one of the authors [illegible] to increase the function of the kidney

known sequelæ polyuria etc have been observed As a characteristic feature may be emphasized an increased functional irritability or an exaggerated response to additional demands

Denervation of the kidneys was also done in animals in which experimental lesions had been induced This included 2 dogs with uranium nephritis and 2 dogs with marked reduction of renal substance by the method of F M Allen and of Mary In both uranium dogs an improvement in urinary and phenolsulphonephthalein output and a decrease in nitrogen retention were noted immediately after denervation In dogs with approximately 35 per cent of remaining renal tissue improved handling of excessive nitrogen *feeding was evident after the operation* Caldwell in rabbits subjected to acute uranium nephritis found no immediate effect from denervation if the operation was performed within four days in other words before spontaneous recovery began

On the clinical side sympathectomy has been *carried out in* 4 patients Decapsulation in addition to the sympathectomy was simultaneously done in the first 2 cases The case reports are as follows

[illegible]

operated upon for a small hydronephrosis and for relief of pain It would seem worth while to try this procedure in cases of chronic nephritis with oliguria and retention It could also be tried early in glomerular nephritis where Volhard believes vasoconstriction to play an important role Milder measures than sympathectomy might suffice for the release of vasoconstriction This might be obtained through the use of diathermy to the regions of the sym pathetic ganglia [illegible] the use of diathermy [illegible] pain in peripheral vasc[illegible] has used the method in the clinic and Eppinger has reported good results abro[illegible] Local anesthes[illegible] at these levels might also prove of value [illegible] and pregan[illegible] This proce[illegible] for periods of at least one month When operation is contemplated preliminary information may be derived either by diathermy by injection of the ganglia or by the use of spinal anesthesia at this level

The interest of the internist in the development of this work is stimulated by the physiologist In a plea for further clinical investigation of the effect of section of the splanchnics on the failing kidney Fulton[6] writes The surgeon then who undertakes to [illegible]

is destroying a part of one of the oldest and most fundamental systems regulating the bodily economy He may be called upon to cut the splanchnic nerve in order to assist the failing kidney or to remove the abdominal sympathetic chain to alleviate the dis tressing symptoms of Hirschsprung s disease

The rationale of these two operations is obvious

REFERENCES

1 [illegible] 1929 [illegible]

[illegible]

4 ELLINGER Ph 1929 Die Absonderung d Harns unter verschiedenen Bedingungen einschliesslich ihrer nervosen Beeinflussung Handb norm u pathol Physiol 4 308–450

5 ELLINGER, Ph AND HIRT A 1925 Zur Funktion d Nierennerven Arch f exp Path u Pharmakol 106 135–208

6 FULTON J F 1930 The physiological basis of the surgery of the sympathetic nervous system New England J Med 203 555–561 587–595

7 HARRIS, S H AND HARRIS, R G S 1930 Renal sympathectomy ton is renal pain and renal sympathectomy Brit J Urol 2 35 –3 4

CASE 4 —(709030) J S N a white male aged twenty-one years

euphyllin ammonium nitrate magnesium sulphate pilocarpine sweats

blood cells +++

TABLE 93

	Right kidney	Left Kidney
Volume cc	10 000	10 000
Specific gravity	1 013	1 015
Albumin grade	2	2
Nitrogen per cent	0 93	0 86
Non protein nitrogen	0 89	0 85
Protein nitrogen	0 04	0 01
Chlorides	0 34	0 33
Casts		
Hyaline	1	Occasional
Granular	1	Occasional
Cellular	1	0
Leukocytes	1 to 9	1 to 7
Erythrocytes	3	3
Phenolsulphonephthalein		
Time of appearance minutes (three to five minutes upper limits of normal)	5	5
Amount per cent	10	6
Indigo-carmine		
Time of appearance minutes (five minutes upper limits of normal)	7	7
Concentration of dye grade	3	3

The results in 3 of these 4 cases are not striking however 2 patients were moribund at the time of operation In the fourth case the clinical condition of the patient with subacute glomerular nephritis is excellent at the present time The third case was

AUTHOR'S INDEX

8 Hess, E 1930 Renal sympathectomy, Pennsylvania Med J, 33, 741–747

& Febiger
13 Legueu, F, and Flandrin, P 1923 Énervation du rein, Presse méd, 31, 741–742
14 Marshall, E K, Jr, and Crane, M M 1922 Studies on the

17 Möllendorff, W v 1929 Anatomie d Nervensystems, Handb d norm u path Physiol, 4, 183–232
18 Müller L R, et al 1924 Die Lebensnerven, 2d ed, Berlin, Julius Springer

AUTHOR S INDEX

8 Hess, E 1930 Renal sympathectomy, Pennsylvania Med J, 33 741–747

9 Heymans, C 1929 Le sinus carotidien, Louvain

10 Hirt, A 1924 Vergleichend anatomische Untersuchungen u d Innervation d Niere, Ztschr f Anat, 73, 621–644

11 Kauffmann, J, and Gottlieb, R 1931 The innervation of the renal parenchyma, Am J Physiol, 96, 40–44

12 Kuntz, A 1934 The Autonomic Nervous System, Philadelphia, Lea & Febiger

13 Legueu, F, and Flandrin, P 1923 Énervation du rein, Presse méd, 31, 741–742

14 Marshall, E K, Jr, and Crane, M M 1922 Studies on the

Physiol, 49, 302–343

16 Milliken, L F, and Karr, W G 1925 The influence of the nerves on kidney function in relation to the problem of renal sympathectomy, J Urol, 13, 1–23

17 Möllendorff, W v 1929 Anatomie d Nervensystems, Handb d norm u path Physiol, 4, 183–232

18 Müller, L R, et al 1924 Die Lebensnerven, 2d ed, Berlin, Julius Springer

examen d un point contesté Compt

kidney, J Urol, 16, 201 200

M

N

O

P

T

U

V

W

Y

Z

GENERAL INDEX.

A

B

S